

2014-1434

In the
United States Court of Appeals
for the Federal Circuit

DEY, L.P., NOW KNOWN AS MYLAN SPECIALTY, L.P.,
and DEY, INC.,

Plaintiffs-Appellees,

v.

TEVA PARENTERAL MEDICINES, INC.,
TEVA PHARMACEUTICAL INDUSTRIES, LTD.,
and TEVA PHARMACEUTICALS USA, INC.,

Defendants-Appellants.

Appeal from the United States District Court for the Northern District of West
Virginia in Case No. 09-CV-87, Judge Irene M. Keeley.

**NON-CONFIDENTIAL BRIEF OF DEFENDANTS-APPELLANTS
TEVA PARENTERAL MEDICINES, INC., TEVA PHARMACEUTICAL
INDUSTRIES, LTD., and TEVA PHARMACEUTICALS USA, INC.**

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1. The full name of every party or *amicus* represented by me is:

Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd., and Teva Pharmaceuticals USA, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd., and Teva Pharmaceuticals USA, Inc.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or *amicus curiae* represented by me are:

The parent corporation of Teva Parenteral Medicines, Inc. is Teva Pharmaceuticals USA, Inc. The direct and indirect parent companies of Teva Pharmaceuticals USA, Inc. are: Orvet UK Unlimited, Teva Pharmaceutical Holdings Cooperative U.A., Ivax LLC (f/k/a IVAX Corporation), Teva Pharmaceuticals Europe, B.V., and Teva Pharmaceutical Industries, Ltd. Teva Pharmaceutical Industries, Ltd. is the only publicly traded company that owns 10% or more of Teva Parenteral Medicines, Inc. or Teva Pharmaceuticals USA, Inc. Teva Pharmaceutical Industries, Ltd. has no parent, and no publicly traded company owns 10% or more of Teva Pharmaceutical Industries, Ltd.

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CONFIDENTIAL MATERIAL OMITTED

Confidential business and formulation information of Defendant-Appellant Teva, Plaintiff-Appellee Dey, and third party Sepracor that is the subject of the District Court’s Protective Order has been redacted from pages 8-10, 18-19, and 29-31.

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TABLE OF ABBREVIATIONS

Teva	Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd., and Teva Pharmaceuticals USA, Inc.
Dey	Dey, L.P., now known as Mylan Specialty, L.P., and Dey, Inc.
Sepracor	Sepracor, Inc. (became Sunovion)
Sunovion	Sunovion Pharmaceuticals, Inc. (was Sepracor)
ALP	Automated Liquid Packaging (became Catalent)
Catalent	Catalent Pharma Solutions (was ALP)
Patents-in-Suit	U.S. Patent Nos. 6,667,344; 6,814,953; 7,348,362; and 7,462,645
'344 patent	U.S. Patent No. 6,667,344
'953 patent	U.S. Patent No. 6,814,953
'362 patent	U.S. Patent No. 7,348,362
'645 patent	U.S. Patent No. 7,462,645
A[number]	Joint Appendix [page]
ANDA	Abbreviated New Drug Application
NDA	New Drug Application
FDA	Food and Drug Administration
Orange Book	The FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations"
Asserted Claims	'344 patent claims 3, 34, 40, 65, 74, 104, 116; '953 patent claims 76, 106, 112, 136, 160, 163; '362 patent claims 1, 2, 3, 4, 6, 8, 9, 10, 12, 15; '645 patent claims 2, 3, 6, 8, 9
POSA	person of ordinary skill in the art
Sepracor Lots	Sepracor Lots 02797A, 01799B, and 03501A
First Lots	Sepracor Lots 02797A and 01799B
First Patent Family	'344 and '953 patents
Second Patent Family	'362 and '645 patents
First Patent Family Asserted Claims	'344 patent claims 3, 34, 40, 65, 74, 104, 116; '953 patent claims 76, 106, 112, 136, 160, 163
Second Patent Family Asserted Claims	'362 patent claims 1, 2, 3, 4, 6, 8, 9, 10, 12, 15; '645 patent claims 2, 3, 6, 8, 9
Arformoterol	An enantiomer of formoterol
LABA	long-acting beta agonist

COPD	chronic obstructive pulmonary disorder
MDI	metered dose inhaler
DPI	dry powder inhaler
LDPE	Low density polyethylene

STATEMENT REQUESTING ORAL ARGUMENT

Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd., and
Teva Pharmaceuticals USA, Inc. request oral argument in this appeal.

STATEMENT OF RELATED CASES

This is an appeal from the United States District Court for the Northern District of West Virginia in Civil Action No. 1:09-cv-00087-IMK. Counsel for Teva are not aware of any other appeal in or from the same proceedings in the District Court previously before this or any other appellate court.

Counsel for Teva are not aware of any case pending in this or any other court that will directly affect or will be directly affected by this court's decision in the pending appeal.

Although not directly related to this case, some of the asserted patents were at issue in *Dey, Inc. v. Sepracor, Inc.*, 847 F. Supp. 2d 541 (S.D.N.Y. 2012). There, the District Court for the Southern District of New York granted summary judgment to Sunovion Pharmaceuticals, Inc. (formerly known as Sepracor, Inc.) that U.S. Patent Nos. 7,348,362 and 7,462,645 (among others) were invalid under 35 U.S.C. §102(b) over the public use of Sepracor's formoterol inhalation solution batch 3501A in clinical trials. *Sepracor*, 847 F. Supp. 2d at 553. Dey and Sunovion then entered into a settlement agreement in which Sunovion stipulated to infringement of U.S. Patent Nos. 6,667,344 and 6,814,953 and judgment was entered on invalidity. (A20658-59.)

Sunovion appealed the District Court's invalidity summary judgment decision to this Court in *Dey L.P. et al. v. Sunovion Pharms., Inc.*, No. 2012-1428

(decided May 20, 2013, by panel Newman, Bryson, and O'Malley), 715 F.3d 1351.

This Court reversed and remanded, finding there were issues of fact whether the clinical trials were a public use. *Sunovion*, 715 F.3d at 1357. After remand, the case settled.

Counsel for Teva are not aware of any other proceedings on the patents here in suit between Dey and Sunovion.

JURISDICTIONAL STATEMENT

The District Court had jurisdiction under 28 U.S.C. §§1331, 1338. The District Court found for Plaintiffs and entered final judgment on March 21, 2014. (A75-76; A27475.) Teva timely appealed on April 17, 2014. This Court has jurisdiction under 28 U.S.C. §1295(a)(1).

STATEMENT OF THE ISSUES

1. Whether the District Court erred as a matter of law in construing “pharmaceutical composition” to exclude stability of the composition.
2. Whether the District Court erred in construing claims 1 and 65 of U.S. Patent No. 6,667,344 and holding that Teva’s ANDA product infringes claims 1 and 65.
3. Whether the District Court erred in construing the claims one way for infringement and another way for validity.
4. Whether the District Court erred in holding that Sepracor Lots were not “on sale” within the meaning of 35 U.S.C. §102(b).
 - a. Whether the District Court erred as a matter of law in holding that the sale of the Sepracor Lots was an “experimental sale.”
 - b. Whether the District Court erred as matter of law in holding that the Sepracor Lots were not prior art because the sales were not “public.”
5. Whether the District Court erred in holding the Asserted Claims not invalid under 35 U.S.C. §§102(b) and 103(a).
6. Whether the District Court erred as a matter of law in failing to consider the doctrine of “simultaneous invention” under 35 U.S.C. §103(a).

STATEMENT OF THE CASE

A. Procedural History

This case arises from Teva's filing of ANDA No. 91-141 with the FDA, seeking approval to market a drug product generic to Dey's Perforomist[®] formoterol fumarate inhalation solution. (A7731-32¶12.) Dey sued Teva for infringement of the Patents-in-Suit under 35 U.S.C. §271(e)(2). (A7734¶28; A7737¶41; A7739¶54; A7741¶67.)

The District Court construed disputed claim terms including "pharmaceutical composition." (A117-18.) Later, the District Court granted Dey's motion for partial summary judgment of infringement. In finding Teva's ANDA product to infringe claims 1 and 65 of the '344 patent (A164-65), the District Court concluded that photostability is irrelevant to stability. (A152 & n.6.) Teva and Dey stipulated to infringement of all other asserted claims, pending appeal. (A166-67.) By agreement of the parties, if the District Court's ruling on summary judgment is overturned, infringement must then be decided for all Asserted Claims. (A166-67.)

Following a bench trial, the District Court entered judgment finding Teva failed to prove the Asserted Claims were invalid. (A75.) Teva appeals this ruling and the partial summary judgment and claim construction decisions. Teva did not earlier appeal the District Court's grant of summary judgment because that

1 year storage time at 5° C, and wherein greater than about 80% of the initial formoterol is present after 1 month usage time at 25° C and 1 year storage time at 5° C.

(A182; A210.) The remaining asserted claims of the '344 patent add compositional details relating to ingredients and proportions, formoterol salts and enantiomers, and packaging and dosage, limitations that are routine formulation optimization. (A182-84; A210-11.) The parties do not dispute that the claim term formoterol refers to racemic mixtures of formoterol, stereoisomers thereof and the single enantiomers of formoterol, including arformoterol. The specifications so state. (A175/4:48-55; A260/4:51-59.) The parties do not dispute that the Asserted Claims cover arformoterol.

Claim 76 of the '953 patent is directed to a method for treating bronchoconstrictive disorders comprising administering a composition equivalent to asserted claim 3 of the '344 patent. (A227.) The remaining asserted claims of the '953 patent include formulation elements and dosages found within the asserted claims of the '344 patent, plus a pH of 5.0. (A182; A225-29; A252-53.)

The Second Patent Family Asserted Claims require a sterile unit dose comprising a formoterol inhalation solution having the same general physical characteristics and specific stability characteristics of the Asserted Claims of the First Patent Family. Claims 8, 9, 10, 12, and 15 of the '362 patent relate to a method of oral administration of formoterol compositions from unit doses. The

asserted claims of the '645 patent relate to a method of treating bronchoconstriction using the unit dose formoterol compositions.

The specifications of all four patents-in-suit are very similar and are collectively referred to as “the specifications.” Pertinent portions thereof are identified by citation to the '344 and '362 patents. (A169-211; A254-69.) The specifications consistently and repeatedly describe the compositions as stable compositions. (A174/2:17-18 (“It is also an object herein to provide more stable formulations”); A174/2:24-27, 42-47; A259/2:23-26, 41-42.) The specifications even describe other formulation excipients and properties (e.g., buffer concentration, ionic strength, storage temperature, and pH) based on their effect on the overall stability of the pharmaceutical composition. (A178/10:13-14, 31-37; A179/11:14-18, 39-41; A264/11:41-43, 62-63; A264/12:40-43; A264-65/12:67-13:2.)

Stability “refers to the length of time at a given temperature that is greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient, e.g., formoterol, is present in the composition.” (A176/5:30-34.) Where required by certain Asserted Claims, e.g., claim 2 of the '344 patent and claim 75 of the '953 patent, the pharmaceutical composition must also be “stable during long term storage,” or have a certain “shelf-life.”

The specifications distinguish and criticize other liquid formoterol compositions because they are not stable. (A174/2:9-12; A259/2:12-14 (“formoterol [is] not adequately stable in aqueous solutions”); A174/2:12-15; A177/7:44-46, 7:65-8:8; A259/2:14-17; A262/7:55-57; A262/8:25-37.)

During prosecution, Dey continually emphasized and relied on the stability of the claimed compositions compared to prior art, leading to allowance of the First Patent Family. (A6659; A6663; A2507.) Dey argued “[t]he cited reference does not disclose **stable, aqueous compositions containing formoterol** formulated at a concentration for direct administration to a subject in need thereof, as required by the instantly-claimed kits.” (emphasis added) (A2507; A2512; A2516.)

Similarly, in responding to Patent Office rejections during prosecution of the Second Family '362 patent, Dey emphasized that it discovered dilute solutions of formoterol which were stable, stating:

Both Gao and Hochrainer *et al.*, cited by the Patent Office, include a very important, but very wrong, teaching: dilute water solutions of formoterol are unstable. The inventors challenged this notion and unexpectedly found that **relatively dilute solutions of formoterol in water are indeed stable**, and with certain modifications and improvements also discovered by the inventors, **could be made even more stable**. In fact, through the inventors' efforts and ingenuity, **aqueous formoterol solutions could be made sufficiently stable to allow them to meet Food and Drug Administration stability standards** and can be marketed, something which requires not just stability, but very rigorous long term stability.

(A12150-51 (emphasis added).)

Dey further argued that in relation to the prior art:

the presently claimed invention represents not only a vast improvement over art which taught away, but even transcends applicants' own discovery, a discovery which was not even in the prior art: **dilute water based formulations could indeed be stable.**

(A12153 (emphasis added).)

Dey referenced both First Patent Family patents during prosecution of the '362 patent. Dey described claim 1 of the '344 patent, as encompassing "both the use of water alone and the use of water in combination with the other aspects of the present invention to form **stable solutions.**" (A12151 n.1 (emphasis added).)

The Patent Office allowed claims in the '645 patent based on the composition's stability: "a **composition** commensurate in scope with the composition of the claims possesses a **stability** such that a shelf life of greater than 90% after 3 months of storage at 25° C and greater than about 96% after 3 months of storage at 5° C." (A7539 (emphasis added).)

Thus, the specifications and prosecution histories emphasize that the pharmaceutical composition must be stable.

C. Formoterol Fumarate Inhalation Solutions Were Known

1. Formoterol and Its Properties Were Known

Formoterol was described in 1976 in Murakami, U.S. Patent No. 3,994,974.

(A11; A285.) Formoterol is a LABA that acts as a bronchodilator useful for

treating bronchoconstrictive disorders, including COPD. (A10-11; A25672-73/214:21-215:11 (Barnes).)

By 1999, formoterol was well-understood and known to degrade by hydrolysis in aqueous solutions. (A11-12.) Refrigeration was known to improve the stability of drugs subject to hydrolytic degradation, including formoterol. (A25597/147:2-13; A25646/188:6-19; A25647/189:3-10; A25650/192:12-18 (Chaudry); A7336/126:3-10, 126:14 (Akapo); A7284-85/226:4-226:11, 226:13-24, 232:18-233:25, 234:21-235:6, 235:9-11 (Pham).) Hydrolytic stability was known to be improved by buffering the solution at an appropriate pH and refrigerating. (A25589-90/139:22-140:3; A25597/147:2-13; A25646-50/188:6-19, 189:3-10, 189:22-190:21, 191:12-18, 192:12-18 (Chaudry); A25810/352:4-6 (Barnes); A14607-08/512:8-514:12 (Pham).) Dey's inventor and both parties' formulation experts agree that stability of an aqueous formoterol solution under given conditions is an inherent property of the solution. (A25601/151:4-17 (Chaudry); A25949-50/488:1-489:4 (Myrdal); *see* A27551-60; A25892-98/431:16-437:19; A26927/1442:2-19 (Hastedt).)

Foradil[®] (formoterol fumarate) DPI product was sold in the late 1990s in Europe, and in 2001 in the U.S. (A25504-05/54:22-55:18 (Chaudry), A26307/841:17-19 (Hendeles); *see* A14324-48; A26199-209/733:10-743:15; A26212/746:9-13.) Foradil[®] delivered a 12 µg dose of formoterol fumarate in the

form of its two stereoisomers, as a dry powder to treat bronchoconstriction.

(A25621-22/163:19-164:7 (Chaudry); A26230-31/764:14-765:7; A26307-

08/841:17-842:5 (Hendeles); A32635-36; A628.) Foradil[®] was widely known, in

part because of its extensive commercial use outside the United States. (A26306-

07/840:23-841:19 (Hendeles); A32636.)

2. Dey and Sepracor Both Developed Formoterol Inhalation Solutions As Formoterol Entered the Public Domain and the Sepracor Lots Were On Sale Prior to the Critical Dates

Formoterol was subject to patent and non-patent exclusivity until the mid-late 1990s. (A25464/14:6-15.) As these impediments were expiring, both Dey and Sepracor worked on formoterol formulations. (A25498-99/48:20-49:7; A25530-32/80:1-82:8 (Chaudry); A7831/227:25-228:5 (Wald).)

In the late 1990s, Sepracor developed an aqueous inhalation solution with arformoterol (formoterol enantiomer) as the active ingredient. (A38.) Sepracor commercialized its inhalation solution as Brovana[®]. (A38.)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3. Packaged Sepracor Lots Were Stable and Ready To Use

The Sepracor Lots contained all the ingredients required by the Asserted Claims: formoterol, citrate buffer, sodium chloride (a tonicity agent), and water (aqueous solution). (A476; A986; A1497; A26149-50/683:7-684:1 (Myrdal).)

The Sepracor Lots were buffered at pH 5 with 5 mM citrate buffer, and were isotonic, with an ionic strength of 0.16. (A26149-50/683:7-684:1 (Myrdal); A476; A986; A1497; A1126; A1769; A1783.)

[REDACTED]

[REDACTED] For Lots 02797A and 01799B, the arformoterol free base concentrations were 0.1 mg/ml (100 µg/ml) and 0.096 mg/ml (96 µg/ml). (A39.) [REDACTED]

[REDACTED]

For Lot 03501A, the arformoterol free base concentration was 0.015 mg/2 ml (7.5 µg/ml). (A40.) [REDACTED]

[REDACTED]

[REDACTED] ALP shipped the packaged drug products to Sepracor for clinical trials and other studies. (A26853-54/1373:23-1374:5; A26842/1362:16-20 (Wald).)

Sepracor Lot 03501A became Sepracor's commercial Brovana[®] product. (A26345/872:18-21 (Hendeles); *Sepracor*, 847 F. Supp. 2d at 547.) The Sepracor Lot compositions are "virtually the same as the scope of the compositions in

[Dey's] patents." (A26150/684:7-8 (Myrdal).) Long-term stability testing on packaged Lots 02797A, 01799B, and 03501A for up to 27 months at 5° C and up to 6 months at 25° C (A1125-30; A1768-72; A1782-96) shows that the packaged Lots meet the stability limitations of the claims:

1. greater than about 97% arformoterol remained after 1 month at 25° C;
 2. greater than about 94% arformoterol remained after 3 months at 25° C;
 3. greater than about 98% arformoterol remained after 3 months at 5° C;
 4. greater than about 97% arformoterol remained after 12 months at 5° C;
- and
5. greater than about 94% arformoterol remained after 24 months at 5° C.

(A26150-51/684:11-685:6 (Myrdal); A1125-30; A1768-72; A1782-96; A39496-501; A39504-06; *Sepracor*, 847 F. Supp. 2d at 547-48.) Arrhenius kinetics projections showed that greater than about 93% of the arformoterol would remain after three years at 5° C. (A26150-51/684:11-685:6 (Myrdal); A1125-30; A1768-72; A1782-96; A39496-501; A39504-06.) Dey admits that Lot 03501A units “were projected to be able to retain over 96% of their formoterol content after 3 years of refrigerated storage” (*Sepracor*, 847 F. Supp. 2d at 547-48.)

4. Dey's Development Was Routine and Led to the Expected Result

Dey began developing an aqueous formoterol inhalation solution in 1999, after Sepracor began its development. (A11; A7831/227:25-228:5 (Wald).) Dey's formulation development studies for formoterol inhalation solution were all routine, and Dey used excipients commonly used in inhalation solutions.

(A25574-77/124:14, 124:22-125:14, 126:4-7, 126:11-18, 126:22-127:7, 127:11-18; A25591/141:17-25 (Chaudry).) Dey's purported "solution" to the stability problem associated with hydrolytic degradation of formoterol in aqueous solutions was to optimize the composition pH for the greatest stability of formoterol, and refrigerate the composition. (A25585/135:10-18; A25596-97/146:20-147:13; A25623-25/165:21-167:18; A25648/190:10-21 (Chaudry); A33416.)

As of filing the First Patent Family, Dey had not determined the dose of formoterol for clinical application. (A25627/169:3-6 (Chaudry).) Dey later settled on the formoterol dose only by performing routine clinical studies (A25627-35/169:3-177:4 (Chaudry); A26260-62/794:2-796:14 (Hendeles); A32379-80; A32466-74), and following the FDA's suggestion to test doses comparable to the known 12- μ g dose in Foradil[®]. (A25846-54/388:5-396:19 (Barnes); A32466-74; A35730-32.)

D. Prior Art Besides The Sepracor Lots Invalidate the Asserted Claims

Aside from the Sepracor Lots, Gao, Murakami, and Foradil[®] are prior art to the Patents-in-Suit. Puigbó, and Gavin are prior art to the Second Patent Family.

1. Published Prior Art

U.S. Patent No. 6,040,344 ("Gao," A1069-79) describes a salt of arformoterol. (A32; A1079/20:33-59.) Gao teaches an aqueous aerosol

formulation for nebulization that has the same ingredients as the composition claimed in the Asserted Claims at pH 5, the most stable pH for formoterol in water:

arformoterol tartrate salt	2 mg
citrate buffered saline citrate buffer sodium chloride water	10 ml
pH	5

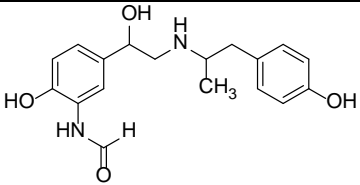
(A1079/20:1-6; A25641-42/183:17-184:18; A25648/190:4-21 (Chaudry); A25778-80/320:6-322:20 (Barnes); A25933-36/472:23-475:4 (Myrdal).) Gao describes the formulation as “quite suitable for short term use” at room temperature, but “not attractive for long term storage” at room temperature. (A1079/20:1-6; A25778-79/320:6-321:6.) The concentration of formoterol as the free base in the exemplified formulation is 139 µg/ml, a concentration suitable for direct administration without dilution or other modification. (A25934/473:14-23 (Myrdal); A26278-79/812:6-813:20 (Hendeles).)

Stability testing and Arrhenius projections on Gao formulations with 5 mM and 50 mM citrate buffer confirm that Gao formulations inherently have the stability required by the Asserted Claims. (A25962-63/501:17-502:23; A25965/504:12-21; A26152-53/686:1-687:12 (Myrdal); A39484-89.)

Gao incorporates by reference Redmon (A1267-74 (U.S. patent); A652-75 (PCT publication)) identified as copending U.S. provisional application 60/061,363. (A1079/20:6-10.) Redmon teaches that aqueous solutions of

formoterol may be refrigerated to provide stability, noting drawbacks to reduced-temperature storage. (A1271/1:53-61.)

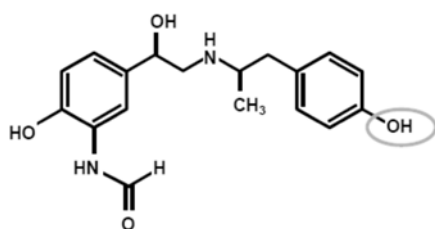
U.S. Patent No. 3,994,974 (“Murakami,” A285-308) discloses bronchodilating agents (A286/1:54-57; A304/38:33-66; A25691-92/233:21-234:6 (Barnes)) and claims formoterol from among the compounds described as effective bronchodilating agents. (A25; A286/1:54-57; A304/38:33-66; A25691-92/233:21-234:6 (Barnes).) Murakami teaches administration “in the form of aerosols as inhalations.” (A289-90/7:65-8:3; A26.) Murakami Example 34 also discloses an aqueous formulation with the same ingredients as the composition in the Asserted Claims except that it contains a formoterol analog rather than formoterol:

	5 mg
sodium chloride	8.5 g
citric acid	1.0 g
water to make	1000 ml
pH	4.0-6.0

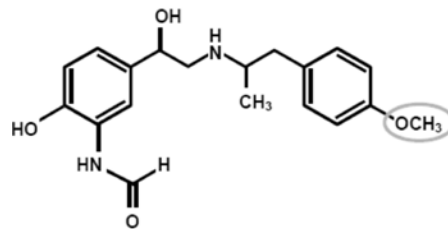
(A25928-31/467:7-470:17 (Myrdal); A304/38:1-9.) Murakami teaches a POSA to dissolve these components in water, adjust the pH, sterilize by filtration, and provide the solution in sealed 1-ml ampoules. (A304/38:10-16.) Each ampoule contains 5 µg/ml of the formoterol analog fumarate salt (A26266/800:5-23

(Hendeles); A25928/467:7-17 (Myrdal)), which is 4.3 µg/ml of the free base (A26054-55/593:20-594:3 (Myrdal)).

Structurally, formoterol and the analog differ only in the substitution of a methoxy group in formoterol for the hydroxy group in the analog (circled, below). (A25929-32/468:13-471:10 (Myrdal); A304/38:1-55.)




Analog



Formoterol

Both formoterol and the analog have similar properties, including degradation by

hydrolysis of the  group. (A25929-32/468:13-471:10 (Myrdal);

A26928/1443:4-7 (Hastedt).) Murakami identifies three compounds as most important – formoterol (Example 22), the formoterol analog in Example 34, and a third compound. (A25928/467:7-17; A286/2:51-57; A304/38:1-16.) Formoterol is the most selective bronchodilator tested by Murakami and is the only compound explicitly claimed in Murakami. (A25925-26/464:19-465:16; A25929-32/468:8-471:20 (Myrdal); A286/2:51-57; A304/38: 33-65.)

Stability testing and Arrhenius projections on a *formoterol* solution prepared according to Murakami Example 34 (as opposed to the formoterol analog) confirm

that the Murakami formoterol formulation inherently has the stability required by the Asserted Claims. (A25962-63/501:17-502:23; A25965/504:12-21; A26152-53/686:1-687:12 (Myrdal); A39481-83.)

Puigbó et al. (“Puigbó,” A1055-1058) treated acute asthma exacerbations by administering unit doses of formoterol fumarate by nebulization. (A25937-38/476:4-477:5 (Myrdal); A26366-67/893:24-894:5 (Hendeles); A1056.) Puigbó formulated a single dose of 12 µg Foradil® formoterol fumarate dry powder in 2 ml of 0.9% sterile saline solution for administration via nebulization to patients. (A1056; A25937-38/476:4-477:5 (Myrdal); A26366-67/893:24-894:5 (Hendeles).) Puigbó’s solution has a pH of about 5.5 and an ionic strength of about 0.16. (A25642/184:5-13 (Chaudry); A25762-63/304:22-305:4 (Barnes); A1056.)

Publication No. WO 01/78745 (“Gavin,” A1686-703) describes a composition comprising 12 µg formoterol fumarate in 2 ml buffered saline solution, which has a pH of about 5.5, for treating respiratory diseases. (A25642/184:5-13 (Chaudry); A25762-63/304:22-305:4 (Barnes); A26365-66/892:22-893:20 (Hendeles); A1687/1:8-11; A1697.)

2. Prior Art COPD and Bronchoconstriction Products

By 1999, inhalation products were available to treat bronchoconstriction (or COPD) administered via nebulization, metered dose inhalers (MDIs), and dry powder inhalers (DPIs). (A26204/738:17-23; A26222-26/756:14-760:15; A26311-

12/845:15-846:4; A26350-63/877:10-890:4 (Hendeles).) Inhalation solutions for nebulization preferably were aqueous, isotonic, included sodium chloride and a buffer such as citrate, and were formulated at a pH optimized for stability of the active. (A25588-90/138:24-140:6 (Chaudry); A26222-26/756:14-760:15 (Hendeles); A426-29; A521; A524-25; A528-29; A532-34; A1041-45; A1046-48; A1154-70; A456/3:48-59.)

Nebulized products packaged in LPDE vials as unit doses of 2-3 ml sterile inhalation solution were well-known before 2000. (*See* A25761-65/303:7-305:9, 306:3-307:3 (Barnes); A26218-26/752:18-760:15; A26350-63/877:10-890:4 (Hendeles); A426-29; A463-64; A467; A521; A524-25; A528-29; A532-34; A1041-45; A1046-48; A1146-49; A1154-70; A538-43.) These unit doses were ready to use—the vial was opened, and the solution was added to a nebulizer without dilution. (A26220-22/754:3-756:13 (Hendeles).) Laminate overwraps to protect unit dose vials from light and other contamination were also known in the art before the critical dates. (A25592-93/142:23-143:11 (Chaudry); A26359/886:3-7 (Hendeles); A14048-49/110:10-111:11, 112:13-113:24 (Pham).) Before April 2000, the FDA required labeling with directions for use. 21 U.S.C. §§352(a)-(f).

Besides Foradil[®], other COPD treatments known to a POSA included Serevent[®], Ventolin[®], Proventil[®], Advair[®], Symbicort[®], Airet[®] and Dulera[®].

(A25738-39/280:17-281:2 (Barnes); A26312-14/846:15-848:14; A26350-63/877:10-890:4 (Hendeles); A426-29; A524-25; A532-34.)

3. Prior Art Compositions Were Stable

Formoterol compositions in the prior art, which have the same components as the Asserted Claims, including the Sepracor Lots, have the same stability as the compositions in the Asserted Claims. (A26152-53/686:1-687:12 (Myrdal).) Dey's Dr. Chaudry admitted that the stability of the claimed compositions is a direct consequence of the components of those compositions: water, formoterol, tonicity agent, and citrate buffer at pH 5, all known before Dey's alleged inventions. (A25588-90/138:21-140:16; A25599/149:1-6; A25601/151:4-17 (Chaudry).) Dr. Hastedt and Dr. Chaudry both agree with Dr. Myrdal that no matter when a composition is made, its stability is the same. (A25601/151:4-17 (Chaudry); A25949-50/488:1-489:4 (Myrdal); A26927/1442:2-19 (Hastedt).)

E. Teva's ANDA Formoterol Fumarate Inhalation Solution

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Formoterol was known, patented, and sold long before Dey applied for the Patents-in-Suit. Dey did not begin developing its formoterol inhalation solution until the formoterol compound patent (Murakami) and exclusivity periods were

nearing expiration. Dey's "development" comprised little more than preparing a standard aqueous formoterol solution and packaging it for cold storage. In securing patent coverage for its development, Dey emphasized the purported stability of its formulation over nearly identical prior art formoterol compositions containing the same ingredients at a pH of about 5. However, Dey's claimed formoterol solution is, itself, not any more stable than prior art formoterol solutions. Dey did not invent a new stable formulation of formoterol - it just wrapped a known unstable formulation in foil to protect it from light and refrigerated it to retard hydrolytic degradation. Just as the person who places milk in the refrigerator has not created a more stable version of milk, Dey did not create a more stable solution of formoterol. Every aspect of Dey's development was routine and obvious, if not anticipated outright, by the prior art.

Underscoring the obviousness of Dey's development, at about the same time, Sepracor independently developed its own formoterol solution for nebulization, a formulation very similar to Dey's. So similar that Dey sued, and now licenses, Sepracor under the very patents it asserts against Teva. Sepracor's simultaneous development of an arformoterol inhalation solution demonstrates that to a POSA there was nothing special, unique, or inventive in Dey's formulation.

Before the critical dates of the Patents-in-Suit, Sepracor purchased finished lots of its formoterol formulation from a third party manufacturer under a sales

agreement. Sepracor used the solutions in clinical trials. These lots were not experimental, and they invalidate the Asserted Claims.

All of the Asserted Claims, as properly construed, require a pharmaceutical composition that is stable irrespective of packaging. Some of the Asserted Claims *further* require that the pharmaceutical composition, irrespective of packaging, meets additional stability requirements, such as being stable during long-term storage or having a particular shelf life. Teva's ANDA product does not infringe the claims as properly construed, because the formoterol solution of Teva's ANDA product is unstable without protective packaging. Nor does the formoterol solution of Teva's ANDA product meet the additional stability requirements relating to long-term storage and estimated shelf life absent protective packaging.

The District Court erred in failing to construe the claims to require a composition that is itself stable, in construing the additional stability requirements to relate to a packaged formoterol solution (as opposed to the solution itself), and in failing to consider Teva's evidence that the formoterol solution of Teva's ANDA product is, itself, unstable. Because the District Court's decision that Teva infringes claims 1 and 65 of the '344 patent was premised on an incorrect claim construction, the decision must be reversed.

That Teva's unpackaged ANDA product is unstable creates a problem for Dey. The Patents-in-Suit were granted based on the stability of its composition,

and yet, if the claims require a stable composition, Teva does not infringe. The District Court held the patents not invalid and infringed. The District Court squared this circle only by incorrectly and inconsistently construing the claims so as not to require a stable pharmaceutical composition for infringement, then changing its construction to require the compositions to be stable and to have “consecutive” stability for invalidity. The Court compounded its claim construction errors by failing to recognize that stability is an inherent property of a formoterol solution, determined by the components of the formulation. Formoterol solutions of the prior art, which have the same components at the same pH as those in the Asserted Claims, inherently have the same stability as the compositions of the Asserted Claims.

ARGUMENT

I. The District Court’s Claim Construction Errors Undercut Its Decisions

The District Court’s constructions are not based on underlying issues of fact and are reviewed *de novo*. *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1292 (Fed. Cir. 2014). The Court’s claim construction errors are fundamental flaws in its analysis, and its decisions must be reversed. The District Court also erred in construing the Asserted Claims differently for validity and infringement. *See Source Search Tech. LLC v. Lending Tree LLC*, 588

F.3d 1063, 1075 (Fed. Cir. 2009). (“[I]t is axiomatic that claims are construed the same way for both invalidity and infringement.”).

A. The District Court Erred in Construing “Pharmaceutical Composition”

1. The Pharmaceutical Composition Must Be Stable

A POSA would understand the term “pharmaceutical composition,” when read in the context of the intrinsic evidence of the Patents-in-Suit to refer to a composition that is, itself, stable. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314-17 (Fed. Cir. 2005) (en banc). The specifications of the Patents-in-Suit and their file histories confirm that stability is an essential element of all Asserted Claims, and the limitation “pharmaceutical composition” refers to a “stable” pharmaceutical composition.

The specifications consistently describe the aqueous formoterol compositions as stable, and criticize other liquid formoterol compositions as not stable. (*See* p. 4, *supra*.) The specifications provide a clear disavowal of unstable pharmaceutical compositions. *AstraZeneca AB v. Mutual Pharm. Co., Inc.*, 384 F.3d 1333, 1340 (Fed. Cir. 2004). The specification's written description of stable compositions characterizes the invention as a whole, not merely a preferred embodiment, and limits the scope of pharmaceutical composition. *Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1330 (Fed. Cir. 2009); *Honeywell Intern., Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1318 (Fed. Cir. 2006).

The prosecution histories confirm this construction. Dey (and the USPTO) characterized the Asserted Claims as directed to stable, aqueous compositions, which were purportedly distinct from the unstable compositions disclosed by prior art. (*See* pp. 5-6, *supra*.) The meaning Dey gave to the claimed “pharmaceutical compositions” to secure allowance cannot be disregarded, yet the Court did, in error. *See Ormco Corp. v. Align Tech. Inc.*, 498 F. 3d 1307, 1316 (Fed. Cir. 2007); *Gillespie v. Dywidag Sys. Int’l, USA*, 501 F.3d 1285, 1291 (Fed. Cir. 2007). The Court acknowledged that Dey “relied on stability coupled with suitability for direct administration” to distinguish its compositions from the prior art. (A102.) That Dey relied on additional aspects of the claims in arguing for patentability does not change the fact that a stable composition is an essential element of all claims.

The District Court’s conclusion that Dey did not “define ‘pharmaceutical composition’ to mean ‘stable composition’ with the reasonable clarity, deliberateness and precision required when an inventor applies his own lexicography” misses the mark. (A101.) Rather, Dey disavowed compositions that are not stable in both the specification and during prosecution. *Thorner v. Sony Computer Entm’t*, 669 F.3d 1362, 1365 (Fed. Cir. 2012) (citing *Vitrionics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1580 (Fed. Cir. 1996).) The specifications in all respects tell a POSA that the claims require a stable composition, buttressed by statements made during prosecution to overcome prior

art rejections. *See Ormco*, 498 F.3d at 1316. By holding that the claimed pharmaceutical compositions encompass compositions that are not themselves stable, the District Court “attribute[d] to the claims a meaning broader than any indicated in the patents and their prosecution history” and “ignore[d] the totality of the facts of the case” *Id.*

B. The District Court Erred in Granting Summary Judgment of Infringement

The District Court erred as a matter of law in holding Teva’s ANDA product to infringe claims 1 and 65 of the ’344 patent. The decision was based on an incorrect claim construction and improperly disregarded evidence. The District Court’s grant of summary judgment is reviewed *de novo*. *Frans Nooren Afdichtingssystemen B.V. v. Stopaq Amcorr Inc.*, 744 F.3d 715, 718 (Fed. Cir. 2014).

1. The District Court Misconstrued Claims 1 and 65

Claims 1 and 65 specify that the aqueous formoterol pharmaceutical composition itself is stable during long-term storage, without packaging. Claim 1 of the ’344 patent includes the specific stability limitation “stable during long term storage” and the limitation “pharmaceutical composition” without reference to packaging.

Re-examined claim 1 of the ’344 patent states:

A pharmaceutical composition, comprising formoterol, or

a derivative thereof, in a pharmacologically suitable [fluid] *aqueous solution*, **wherein the composition is stable during long term storage**, [the fluid comprises water, and] the composition is formulated at a concentration *effective for bronchodilation by nebulization*, and the composition is suitable for direct administration to a subject in need thereof, *without propellant and without dilution of the composition prior to administration*.

(A210/1:31-39 (bracketed terms deleted and italicized terms added during reexamination) (emphasis (**bold**) added).) The antecedent for the term “composition” in the phrase “wherein the composition is stable during long term storage” is the “pharmaceutical composition.” Claim 1 requires the pharmaceutical composition itself, which is an aqueous solution that must be stable, to also be “stable during long term storage.” Claim 1 contains no packaging limitation.

Claim 65, which recites an article of manufacture comprising the aqueous composition of claim 1, specifically describes packaging as a *separate element* of the article of manufacture. Claim 65 provides:

An article of manufacture, **comprising packaging material, an aqueous composition comprising the composition of claim 1 formulated for single dosage administration**, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with an undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for the treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

(A184/21:27-36 (emphasis (bold) added).)

Claim 65 separates “aqueous composition” and “packaging material” into two elements, clarifying that the aqueous composition is the composition of claim 1. As stated in *Phillips*, “the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim.” 415 F.3d at 1314-15. There is nothing in the claims to rebut this presumption.

Not only has Dey embraced the construction that the composition does not include packaging – having proposed that the term “pharmaceutical composition” means “a medicinal formulation containing an active drug and inert excipients,” – the Court adopted that construction of composition with no mention of packaging. (A95-103.) Similarly, the parties agreed that “stable during long term storage” means an estimated shelf life of greater than 1, 2, or 3 months usage time at 25° C and greater than 1, 2, or 3 years storage time at 5° C (A118) without reference to packaging. The District Court also pointed out that Dey agreed that the claimed *compositions* were stable. (A100.)

The specification of the '344 patent only refers to packaging as separate from the composition: “Articles of manufacture, containing packaging material, a composition provided herein ... and a label ... are also provided” (A175/4:27-35); and provides a laundry list of suitable packaging. (A177/8:25-33; A181/16:53-61.)

But the specification does not mention packaging for improving stability by protecting the composition from light. The only stability test described in the '344 patent involves formoterol solution in scintillation vials. (A182/17:36-47.) The claimed stability is of the composition itself, independent of light-protective packaging.

The term “pharmaceutical composition” must be construed identically in all four Patents-in-Suit. (A95-103.) Claims to a protective laminate overwrap in the Second Patent Family '645 patent support this construction. Such claims would be superfluous if the “pharmaceutical composition” already included packaging.

2. Photostability Is Relevant to Long-term Stability

The District Court erred in holding photostability irrelevant to long-term stability. The Court reasoned that the specification defines stability as “includ[ing] two independent variables, time and temperature, and one dependent variable, the percentage of the initial amount of active ingredient present in the composition following a period of storage.” (A152.) The Court then incorrectly held photostability “irrelevant” because “exposure to light and/or ultraviolet (“UV”) radiation is simply not part of that definition.” (A152.)

A POSA would recognize that confirmatory photostability studies are a “necessary aspect of stability testing.” (A23304; A23328-29.) Such testing is “undertaken to provide the information necessary for the handling, packaging and

labeling” of drug products and dosage forms. (A23332.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Dey also argued for the patentability of its invention because the claimed aqueous formoterol solutions could be made sufficiently stable “to allow them to meet Food and Drug Administration stability standards” (A12150-51.) [REDACTED]

3. Dey Presented No Evidence that Teva’s Formoterol Fumarate Solution Is Stable Absent Protective Packaging

A composition that is, itself, not stable does not infringe properly-construed claims 1 or 65, even if packaged in a protective overwrap. Dey presented no evidence that Teva’s inhalation solution is, itself, “stable during long term storage” according to claim 1. [REDACTED]

[REDACTED] Dey’s tests are not probative of infringement of the claims as properly construed. Dey was not entitled to judgment as a matter of law. *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1326 (Fed. Cir. 2007) (“Summary judgment is appropriate [only] where there is no genuine issue of material fact and the moving party is entitled to a judgment as a matter of law.”).

A23326-38.)

Teva’s evidence demonstrates a genuine issue of material fact sufficient to preclude summary judgment. *See Ortho-McNeil Pharm.*, 476 F.3d at 1326 (“...drawing all justifiable inferences in favor of the non-moving party, the evidence is such that a reasonable [fact-finder] could return a verdict for the non-movant”). The District Court improperly disregarded Teva’s evidence based on its erroneous view that photostability was irrelevant. (A152 n.6.)

C. The District Court’s New Construction of Stability In Assessing Invalidity Undermines Its Infringement Decision

The parties agreed to the meaning of “stable during long term storage” (A118) and this was the construction the District Court applied at summary judgment. (A124.) This construction defined shelf life in terms of one set of time and temperature conditions and storage time in another set of time and temperature conditions. Shelf life and storage time are defined as separate, unrelated stability requirements. When deciding invalidity, the Court altered this agreed-upon definition, stating: “Dey’s patents require that at least 80% formoterol remain after *consecutive* storage conditions of ‘one year at 5°C and one month at room temperature.’” (A16-17 (emphasis added).)

By now requiring that the shelf life and storage time requirements occur *consecutively*, there is no basis for the Court's holding that Teva's ANDA

inhalation solution (or its product) infringes the patents, and, in particular, claim 65. Dey did not present evidence that Teva's ANDA inhalation solution, or its packaged product, have the construed *consecutive* shelf life and storage time. ■

██████████ Having adopted a new claim construction, the District Court’s prior infringement holding must be reversed.

More broadly, the District Court was inconsistent in construing stability of the claimed compositions. The Court declined to construe “pharmaceutical composition” (present in all Asserted Claims) as a “stable composition.” The Court also disregarded Teva’s evidence that the formoterol solution comprising Teva’s ANDA product is, itself, unstable absent packaging. The Court was erroneously persuaded that “Dey never asserted that its pharmaceutical compositions had an inherent characteristic of ‘stability’ distinct from being ‘stable during long term storage,’” even though the long-term storage limitation is not present in all Asserted Claims. (A153; A103.) Paradoxically, in its validity analysis, the Court implicitly construed all Asserted Claims to require a stable composition, by distinguishing prior art because all Asserted Claims require “an aqueous formulation of formoterol with long-term stability.” (A58-60; A54-55; *see* A28 n.5.) The Court’s error in failing to construe the claims the same way

when analyzing infringement and validity is fatal to its decisions. *Source Search Tech.*, 588 F.3d at 1075.

II. The District Court Erred in Finding that the Sepracor Lots Were Not “On Sale”

ALP sold batches of arformoterol inhalation solution to Sepracor more than one year before the priority dates of the Patents-in-Suit. The District Court incorrectly dismissed these sales as the provision of services by a packager (A42-44), when instead ALP made and sold finished packaged drug product to Sepracor. (A26842-43/1362:4-1363:8 (Wald).) Without ALP’s conversion of arformoterol to an inhalation solution, Sepracor would not have had a finished drug product for its clinical trials. (A26842/1362:4-20 (Wald).) The District Court also misapplied the law of “on sale,” improperly relying on the experimental use exception, and requiring the sale to be public. (A43; A45.)

A. Legal Standards

An invention is “on sale” when the claimed invention was both (1) the subject of a commercial offer for sale before the critical date and (2) “ready for patenting.” *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 67 (1998). A commercial offer for sale is determined by applying traditional contract law principles, *Allen Eng’g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1352 (Fed. Cir. 2002), and occurs when “the buyer pays or promises to pay the seller for the thing bought or sold.” *Zacharin v. U.S.*, 213 F.3d 1366, 1370 (Fed. Cir. 2000) (citation omitted).

An invention is considered “ready for patenting” when it has been reduced to practice (e.g., manufactured) or when it has been described with sufficient specificity to enable one of ordinary skill to practice the invention. *Pfaff*, 525 U.S. at 67-68; *see also Abbott Labs. v. Geneva Pharms.*, 182 F.3d 1315, 1318 (Fed. Cir. 1999). Whether a patent is invalid because the invention was on sale is a question of law based on underlying facts. *See Hamilton Beach Brands, Inc., v. Sunbeam Prods., Inc.*, 726 F.3d 1370, 1375 (Fed. Cir. 2013). This Court reviews *de novo* whether an invention was on sale within the meaning of §102(b) and reviews the factual findings for clear error. *See id.*

B. The Sepracor Lots Were On Sale

The Sepracor Lots were “ready for patenting,” as they were manufactured and used in clinical trials. (A26842/1362:4-20 (Wald).) *See Abbott Labs.*, 182 F.3d at 1318. The Lots embodied features of the claimed inventions. (*See* A26149-50/683:8-684:8 (Myrdal).) The issue is whether the Lots were the subject of a commercial offer for sale. They were.

1. The Transactions Between ALP and Sepracor Were Commercial Sales

The District Court erred in concluding that the agreements between ALP and Sepracor were “contract[s] for services,” not sales. (A42-43.) ALP manufactured the inhalation solutions of the Lots according to Sepracor’s specifications, and delivered finished drug product to Sepracor for a price. (A7821/35:14-23;

A26842-43/1362:4-1363:8 (Wald).) ALP’s acceptance of Sepracor’s purchase orders before the critical dates of the Patents-in-Suit shows that ALP offered the Lots to Sepracor in a commercial sale. (A7821/35:14-23; A26840-41/1360:15-1361:3; A26849/1369:17-25 (Wald).) *See Hamilton Beach*, 726 F.3d at 1376 (“[A] commercial offer for sale under §102(b) is ‘one which the other party *could* make into a binding contract by simple acceptance.’” (quoting *Grp. One, Ltd. v. Hallmark Cards, Inc.*, 254 F.3d 1041, 1048 (Fed. Cir. 2001))) .

The District Court concluded that the Sepracor/ALP transactions were not sales because Sepracor provided the arformoterol (and sometimes certain other raw materials) to ALP. (A43-44.) The District Court’s reasoning is beside the point. A commercial sale occurs even if a party “had ownership rights in the invention when an embodiment thereof was produced and sold to [that party].” *Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp.*, 182 F.3d 888, 891 (Fed. Cir. 1999) Even if Sepracor owned the arformoterol at the time of the sale, Sepracor purchased finished product – packaged arformoterol inhalation solution – from ALP. ALP did not simply “package” what Sepracor provided. ALP converted whatever ingredients Sepracor provided – with ingredients ALP provided – into an inhalation solution that did not exist previously, and then packaged and delivered this new product to Sepracor for an agreed price. (A7821/35:14-23; A26840-41/1360:15-1361:22; A26847-49/1367:18-1369:25 (Wald).)

2. The Lots Were Not Experimental

According to the District Court, because Sepracor used the Lots exclusively for clinical trials, the primary purpose of the sale was experimental, not commercial. (A43.) The District Court is wrong. The primary purpose of the ALP-Sepracor agreement was commercial—supplying finished goods for a price. As this Court held in *Zacharin*, “A contract to supply goods is a sales contract . . . regardless of whether the goods are to be used for testing in a laboratory or for deployment in the field.” 213 F.3d at 1370.

The experimental use exception applies only where the primary purpose of the use is to perfect the claimed invention. *See Allen Eng’g*, 299 F.3d at 1354. Here, the primary purpose of Sepracor’s clinical trials was not to perfect the “invention.” Sepracor’s “invention” was already “ready for patenting.” (A26842/1362:4-20 (Wald).) The clinical trials were to determine FDA safety and efficacy of a completed invention (A7825-27/141:17-148:03 (Wald); A1778), a determination akin to market testing to gauge consumer demand for a specific purpose. *See Dippin’ Dots, Inc. v. Mosey*, 476 F.3d 1337, 1344 (Fed. Cir. 2007) (citing *In re Smith*, 714 F.2d 1127, 1135 (Fed. Cir. 1983)).

3. An Invalidating Sale Need Not Be Public

The District Court incorrectly concluded that the on-sale bar “is not triggered when a third party, unaffiliated with the inventor, sells a non-public

invention in a manner that does not give the public access to the transaction.”

(A45.) However, secret sales activity even by one other than the inventor triggers the on-sale bar. *See Brasseler*, 182 F.3d at 891 (citing *In re Caveney*, 761 F.2d 671, 675-76 (Fed. Cir. 1985)).

The District Court apparently reached an incorrect conclusion based on *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). However, this Court explained that *W.L. Gore* “does not support the broad proposition that the ‘secret’ commercialization of an invention by a third party creates no bar.” *J.A. LaPorte, Inc. v. Norfolk Dredging Co.*, 787 F.2d 1577, 1582 (Fed. Cir. 1986). In *J.A. LaPorte*, this Court found that when a third party copied and sold an invention more than one year before the inventor filed for a patent, with no public disclosure, the purchase arrangement between the third party and its buyer created an on-sale bar for the inventor’s patent. *Id.* at 1581-82. As this Court explained, “the question is not whether the sale, even a third party sale, ‘discloses’ the invention at the time of the sale, but whether the sale relates to a device that embodies the invention.” *Id.* at 1583 (citations omitted). The Sepracor Lots relate to inhalation solutions embodying the invention, or obvious variants thereof. (*See* pp. 37-39, *infra*.)

4. The Lots Are Prior Art to the Claimed Invention

The inhalation solutions ALP sold to Sepracor are prior art to the claimed invention because they were “on sale” prior to the critical dates of the Patents-in-Suit. Lots 02797A and 01799B are prior art to the First Patent Family Asserted Claims and the Second Patent Family Asserted Claims. Lot 03501A is prior art to the Second Patent Family Asserted Claims. (A26149-50/683:8-684:8 (Myrdal).) *See Dippin’ Dots*, 476 F.3d at 1344 (“Prior art under the §102(b) on-sale bar is also prior art for the purposes of obviousness under §103.”).

Dey and Sepracor agreed that Brovana[®], which has the identical composition to Lot 03501A, infringes at least asserted claims 2, 3, 6, 10, 12, and 15 of the ’362 patent and asserted claims 3 and 8 of the ’645 patent. (A25195; *Sepracor*, 847 F. Supp. 2d at 547.) The sale of Lot 03501A is a sale of an embodiment of those asserted claims and of the remaining asserted claims (’362 patent claims 1, 4, 8, and 9; ’645 patent claims 2, 6, 9.) (*See* pp. 8-11, *supra*; A26150/684:4-8 (Myrdal); A26239-44/773:16-774:18, 775:7-778:4; A26253-55/787:19-789:2, 789:13-22; A26257-58/791:24-792:7; A26377-83/904:23-910:12; A26386-88/913:4-915:17; A26408/935:12-17 (Hendeles).)

If properly considered as prior art, Lot 3501A anticipates the Second Patent Family Asserted Claims and the First Lots anticipate or render obvious the First Patent Family Asserted Claims.

The District Court erred in finding the First Lots do not disclose the stability limitations of the First Patent Family Asserted Claims. (A47-48.) The District Court's finding overlooked the inherent stability of the First Lots, and was clearly erroneous. (A25588-90/138:21-140:16; A25599/149:1-6; A25601/151:4-17 (Chaudry); A25949-50/488:1-489:4 (Myrdal); A26927/1442:2-19 (Hastedt).) The First Lots include all the ingredients required by claims 3 and 34 of the '344 patent and claims 76 and 106 of the '953 patent. The additional asserted claims ('344 patent claims 40, 65, 74, 104, and 116; '953 patent claims 112, 136, 160, and 163) add only obvious variations that do not affect stability. (*See* pp. 8-11, *supra*; A26149-50/683:8-684:8 (Myrdal); A26262-65/796:15-799:15; A26281-83/815:17-817:22; A26291/825:4-16; A26293-95/827:21-828:14, 829:7-22; A26298-99/832:13-833:4; A26302-04/836:14-838:11; A26323-24/857:11-858:14; A26374-77/901:18-904:22; A26390-403/917:4-930:5; A26406-08/933:1-935:17 (Hendeles).) The inherent stability of the Lots is compelling: "If a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics." *See Abbott Labs.*, 182 F.3d at 1319.

The method claims require nothing more than the expected outcome of treating bronchoconstrictive disorders when the compositions of the Sepracor Lots

were used as intended. The method claims are invalid in view of prior art compositions for the same reasons the composition claims are invalid. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 424 F.3d 1276, 1285 (Fed. Cir. 2005) (“[A]n article of manufacture in the prior art can be used to support an anticipation rejection of method claims that ... define what happens when that article of manufacture is placed in the environment in which the article will be used.” (citing *In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986))). The Sepracor Lots were intended for use to treat bronchoconstrictive disorders including COPD, and are prior art to the claimed methods.

5. Simultaneous Invention Establishes the Obviousness of the Patents-in-Suit

Even if the Sepracor Lots were not “on sale,” they and Puigbó and Gavin (*see* pp. 8-11, 16, *supra*) are evidence of the simultaneous invention of the Asserted Claims. The District Court erred in failing to consider simultaneous invention in its obviousness analysis for either Family. The Sepracor Lots are highly probative, if not conclusive, evidence that the Asserted Claims would have been obvious to a POSA. Alleged inventions, made within a comparatively short space of time of each other by different parties, are persuasive evidence that the supposed “invention” was the product only of ordinary skill in the art and is not inventive. *Geo. M. Martin Co. v. Alliance Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1305-1306 (Fed. Cir. 2010) (citations omitted). Near-simultaneous invention can

serve as evidence of obviousness. *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000).

The Sepracor development of Brovana[®] – a product admittedly covered by the Asserted Claims – is objective evidence that Sepracor independently conceived and reduced to practice the same “invention” as Dey at about the same time as Dey. Given that Dey and Sepracor stipulated that Brovana[®] infringes all four patents-in-suit (A20657-58; A25195), the simultaneous creation by Sepracor of an arformoterol aqueous inhalation solution suitable for direct administration without further modification leaves no doubt that the alleged inventions of the Asserted Claims would have been obvious to a POSA.

III. Dey's Patents Claim Only What Was Already Known in the Art Even Ignoring the Sepracor Lots

Dey's patents posited the problem of an aqueous formoterol solution having long-term stability. (A174/2:12-15; A259/2:14-17.) Dey allegedly solved the problem by (a) making an aqueous formoterol saline solution, buffered at about pH 5 with a citrate buffer, and (b) refrigerating the solution. (A25595-99/145:12-149:6 (Chaudry).) *Under packaging and refrigeration*, the composition was sufficiently long-term stable, according to the definition of stability Dey arbitrarily created in its patents. (A25595-99/145:12-149:6 (Chaudry).) However, Dey did nothing new.

Gao and Murakami both taught aqueous formoterol formulations buffered with a citrate buffer at pH 5.0 (Gao) or 4-6 (Murakami). (A1079/20:1-3; A304/38:1-9.) Such aqueous formoterol solutions were known to degrade by hydrolysis—and *were not considered to be long-term stable at room temperature*, but Gao pointed out that short term stability at room temperature was satisfactory. (A11-12; A1079/20:3-6.) Likewise, Gao recognized that refrigeration increased the storage time for aqueous formoterol solutions. (A1079/20:6-10; A1271/1:53-61.) Decreasing the temperature to lengthen the shelf life of solutions that degrade due to hydrolysis was well-known in the art. (A25650/192:12-18 (Chaudry); A25810/352:4-6 (Barnes).) That Gao (or Redmon) sought an alternative to refrigeration for a formoterol inhalation solution does not alter that refrigeration was a viable and known way to increase the shelf life of formoterol solutions.

The Asserted Claims are obvious not merely because Dey used standard techniques to arrive at the claimed inventions. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367-68 (Fed. Cir. 2007). They are obvious because Dey achieved only the expected results of using those standard techniques. *See In re Applied Materials, Inc.*, 692 F.3d 1289, 1297-98 (Fed. Cir. 2012). The result of Dey's research was a composition having the same ingredients at about the same pH and having the same stability as prior art aqueous formoterol fumarate formulations. (A25601/151:4-22; A25641-42/183:17-184:18 (Chaudry); A25778-80/320:6-

322:20; A25798-802/340:9-344:9 (Barnes); A25946-50/485:21-489:11 (Myrdal); A1069-79; A285-308.) This was expected; achieving the claimed long-term storage and shelf life required refrigeration and foil overwrap, just like prior art compositions. (A25584-85/134:25-135:17; A25595/145:12-20; A25598/148:14-18 (Chaudry).) Dey did not accomplish the uniquely stable aqueous formoterol *solution* it proclaimed to the PTO. All Dey did was re-characterize the inherent stability of formoterol solutions in a new way.

Dey's test-driven claiming of an inherent property of prior art formulations in a new way does not make its formulation patentable. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012); *see also Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1368 (Fed. Cir. 2006) (“[A] newly discovered property of the prior art cannot support a patent on that same art....”). Similarly, optimizing a composition and packaging it as a unit dose, with a known dosage strength, are merely routine steps known to those of ordinary skill in the art that do not confer patentability. (A25591/141:17-25 (Chaudry); A26231/765:8-16; A26287-89/821:17-822:8; A26304-05/838:12-839:9; A26375/902:2-13 (Hendeles).) *See Applied Materials*, 692 F.3d at 1295 (quoting *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955)).

The claimed formoterol concentration ranges are presumed to be obvious because they fall within the disclosures of the prior art. *Iron Grip Barbell Co. v.*

USA Sports, Inc., 392 F.3d 1317, 1322 (Fed. Cir. 2004). Dey never rebutted the presumption by showing the prior art taught away from the claimed invention or that new and unexpected results are achieved by formoterol concentrations in the claimed range. *Id.* Not only was the concentration of formoterol fumarate in Perforomist[®] suggested by the FDA, the final concentration was determined by routine clinical trials, years after the patent applications were filed. (A25628-29/170:25-171:3; A25631-32/173:15-174:24 (Chaudry); A25846-54/388:5-396:19 (Barnes); A32466-74; A35730-32.) Dey presented no evidence that anything about the claimed formoterol concentrations is critical to the invention or yields unexpected results. *See In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996); *In re Aller*, 220 F.2d at 456.

A. The District Court Misapplied the Law of Obviousness

Patent claims are invalid when the differences between the claimed invention and the prior art “are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.” 35 U.S.C. §103(a). When a patent claims known elements, used for the same purposes as in the prior art, the combination “is likely to be obvious when it does no more than yield predictable results.” *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 416 (2007). Obviousness is a legal determination based on underlying factual inquiries: (1) the scope and content of the prior art, (2) the level of ordinary

skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). This Court reviews *de novo* the District Court’s ultimate legal conclusion of whether the claimed invention would have been obvious and reviews the underlying fact-findings for clear error. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354 (Fed. Cir. 2013). The parties generally agree as to the level of ordinary skill in the art. (A55.)

The Court mistakenly looked for specific disclosure of stability in prior art formulations, while ignoring the inherent stability of prior art solutions. The Court failed to even consider the near-simultaneous conception and reduction to practice by Sepracor and others, and it failed to consider the sales of Sepracor Lots as prior art. The Court incorrectly found that prior art “teaches away” from the Asserted Claims.

B. Any Differences Between the Claimed Inventions and the Prior Art Are Trivial and Within the Level of Ordinary Skill

The Asserted Claims are directed to compositions and methods including known formoterol dosage strengths, known buffer concentrations, known volumes, known packaging, and known labels. Each element of the Asserted Claims is used for the same purpose and the same function as in the prior art, achieving no better results than what was reasonably expected from the prior art. This combination of familiar elements via known methods yields predictable results and would have

been obvious to a POSA. *KSR Int'l*, 550 U.S. at 416.

Dey admits that routine techniques for preparing an inhalation solution formulation were known. (A25577/127:11-18 (Chaudry).) These techniques included assay development and studies of solubility, pH studies, buffer species stability, buffer concentration stability, ionic strength stability, and active concentration stability. (A25574-78/124:11-128:24 (Chaudry).) Routine dose-ranging studies also were used to find an effective and safe dose. (A25834/376:13-22 (Barnes); A26231/765:8-16 (Hendeles).) Using these known techniques achieved the expected result.

Sepracor's near-simultaneous development of a formoterol inhalation solution illustrates that a POSA was not only motivated to make an aqueous formoterol inhalation solution but had a reasonable expectation of doing so. Neither Dey nor Sepracor could have marketed a formoterol inhalation solution in the U.S. until the Murakami patent, and other non-patent exclusivities, expired. (A25464/14:6-15.) *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (patent and non-patent exclusivities prevented others from entering the market). Once the patent and regulatory hurdles were gone, both Dey and Sepracor developed refrigerated aqueous formoterol inhalation solutions for nebulization. (A25504-05/54:2-55:18 (Chaudry); A25757-58/299:9-300:3 (Barnes); A26625-26/1145:16-1146:2 (Graybill); A20656-65; A25194-97.)

C. The First Patent Family Asserted Claims Are Invalid in View of Prior Art

The First Patent Family Asserted Claims are taught by the prior art. A POSA would have been motivated by prior art to make an aqueous formoterol inhalation solution, and would have reasonably expected to succeed. The composition, formoterol concentration and other claim limitations were taught to a POSA, as described below.

1. Pharmaceutical Composition Comprising Formoterol in a Pharmacologically Suitable Aqueous Solution, Without Propellant Is Taught by the Prior Art

Each of Gao and Murakami teaches a propellant-free pharmaceutical composition comprising formoterol in a pharmacologically suitable aqueous saline solution. (A1079/20:1-3; A304/38:1-9; A25928-36/467:6-475:4 (Myrdal).) By 2000, a POSA knew 12 µg formoterol fumarate dihydrate was used in dry power inhalers and knew that formoterol was the only Murakami compound used commercially. (A25932/471:11-20 (Myrdal); A25504-05/54:22-55:18 (Chaudry); A26306-08/840:14-16, 841:17-842:5 (Hendeles).) Murakami taught a POSA that the bronchodilator compounds could be administered by inhalation, and pointed to formoterol as a preferred compound. (A289/7:65-8:3; A26.) A POSA would have known that the solution of Murakami Example 34 was *suitable* for administration by nebulization and would have been motivated to use formoterol in that solution for nebulization. (A26246/780:6-19 (Hendeles).)

2. Formulated at a Concentration Effective for Bronchodilation by Nebulization and Suitable for Direct Administration by Nebulizer Without Dilution Is Taught by the Prior Art

A POSA knew that Gao disclosed nebulization solutions containing 139 µg/ml arformoterol, measured as the free base, and that Gao did not mention dilution before administration. (A25934/473:14-23 (Myrdal); A26278-79/812:6-813:20 (Hendeles).) A POSA also knew that Murakami taught formoterol and a composition comprising 4.3 µg/ml formoterol analog, measured as the free base. (A304/38:1-16, 38:33-66; A25928-31/467:7-470:17; A26054-55/593:20-594:3 (Myrdal).) A POSA also knew that both concentrations were effective for bronchodilation by nebulization and suitable for direct administration by nebulizer without dilution. (A25934/473:14-23 (Myrdal); A26266/800:5-23; A26278-79/812:6-813:20 (Hendeles).) The concentrations disclosed in Gao and Murakami are within the range of about 5 µg/ml to 2,000 µg/ml described in the First Patent Family. (A25934/473:14-23 (Myrdal); A26266/800:5-23; A26278-79/812:6-813:20 (Hendeles); A177/8:46-48.)

The formoterol free base concentration range claim limitations of (i) about 5 µg/ml to about 10 µg/ml or (ii) about 5 µg/ml to about 50 µg/ml in the re-examined claims (A210-11; A252-53) are not expressly described in the specification of the First Patent Family. They represent nothing more than design choices driven by the FDA. When the application leading to the '344 patent was

filed, Dey did not know the effective concentration of formoterol. (A25626-27/168:24-169:17 (Chaudry).) The formoterol dose in Perforomist[®] was determined much later, through clinical studies. (A25628-30/170:25-172:18; A25631-32/173:15-174:24 (Chaudry).) Importantly, the formoterol dose claimed in the reexamined claims resulted from the FDA's suggestion that Dey should test lower doses, comparable to the 12 µg dose in Foradil[®]. (A25846-54/388:5-396:19 (Barnes); A35730-32.)

The range of 5 µg/ml to 2,000 µg/ml disclosed in the First Patent Family specifications informs a POSA that all concentrations within the range are equivalent to one another. The First Patent Family does not teach (or show that the inventors appreciated) any critical difference between formoterol concentrations of 5 µg/ml and 2,000 µg/ml, or at any other concentration or range in between. Nor has Dey shown criticality or unexpected results for the narrower range now found in some of the reexamined claims. Formoterol concentration ranges described in the First Patent Family specifications encompass both the claimed formoterol concentrations and those of Gao and Murakami. (A177/8:46-52.)

A POSA would have been motivated to use 10 µg formoterol in 2 ml of formulation, resulting in a 5 µg/ml concentration, and would have expected the solution to be suitable for administration without dilution. The prior art taught inhalation solutions having unit dose volumes of 2 ml for nebulization, by direct

administration and without dilution (A26276/810:10-18 (Hendeles)), and the Foradil[®] formoterol dose of about 10 µg was known to be effective to treat asthma and COPD. (A26276/810:10-18.) An inhalation solution having a 5 µg/ml formoterol concentration as in claims 40, 104, and 116 of the '344 patent and claims 112, 160, and 163 of the '953 patent would have been obvious to a POSA. A POSA would have determined an effective dose of formoterol as a routine part of clinical trials and would have expected to successfully prepare a formulation containing that effective dose. (A25631-32/173:15-174:20 (Chaudry); A26231/765:8-16 (Barnes).) The narrower claimed dosage range in the reexamined claims would have been obvious to a POSA. The mere optimization of known variables, such as formoterol dose, is obvious where there is no showing of anything unpredictable or unexpected. *See, e.g., Applied Materials*, 692 F.3d at 1297-98.

3. Stability, Shelf Life, and Degradation Rate Are Met by the Prior Art

The formulations taught in Gao and Murakami have the same ingredients and same pH as the claimed compositions, and thus have the same inherent stability (including “stable during long term storage”), shelf life (“estimated shelf life of greater than 1 month usage time at 25° C and greater than or equal to 1 year storage time at 5° C”), and degradation rate (“greater than about 80% of the initial formoterol is present after 1 month usage time at 25° C and 1 year storage time at

5° C”) as required by the claims, if the claims are directed to light-protected solutions. (A25949-50/488:1-489:4 (Myrdal); A26266-68/800:5-801:7; A26277-79/811:16-813:6; A26320-23/854:18-857:6; A26390-93/917:24-920:15 (Hendeles).) Gao even teaches that its formulation is suitable for short term storage at room temperature and that refrigeration extends shelf life. (A1079/20:1-10.) Dr. Myrdal’s analysis of stability testing on a formoterol solution prepared according to Murakami Example 34 and on two formoterol solutions prepared according to Gao with 5 mM and 50 mM buffer concentrations confirm these formulations inherently have the stability required by the Asserted Claims. (A25962-63/501:17-502:23; A25965/504:12-21; A26152-53/686:1-687:12; A26137-38/671:18-672:3 (Myrdal); A39481-89.)

The District Court held that inherency *is not* relevant to obviousness. (A62.) The District Court was wrong, and its error was not harmless. Inherency relates to obviousness. *See, e.g., Santarus*, 694 F.3d at 1354 (holding that an obvious formulation cannot become patentable merely by testing and claiming an inherent property.); *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995); *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011). The claim limitations relating to stability, long-term storage, and shelf life are not patentably significant. As Dr. Chaudry admitted, stability and shelf life are properties necessarily present in the claimed compositions. (A25599/149:1-6; A25601/151:4-22.) *See Alcon Research, Ltd. v.*

Apotex Inc., 687 F.3d 1362, 1369 (Fed. Cir. 2012) (citing *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009)). Where, as here, the prior art teaches compositions having the same components as the claimed compositions, measuring an inherent property of the compositions is not inventive. *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249 (1945) (“It is not invention to perceive that the product which others have discovered had qualities they failed to detect.”).

The District Court’s finding that stability testing done on the “Murakami” and “Gao” solutions is unreliable due to the choice of buffer concentration and the removal of oxygen does not inform the obviousness analysis, but it is clearly erroneous. (A29; A37.) Oxygen was known to have little effect on hydrolytic degradation, the known primary degradation route of formoterol. (A26163/697:7-21; A26187-88/721:22-722:7 (Myrdal).) Testing the Gao formulation prepared with two standard buffer concentrations, 5 mM and 50 mM, bracketing the claimed 20 mM concentration (’344 patent claim 74; ’953 patent claim 136), had no appreciable effect on stability. (A25962-63/501:17-502:23; A26137-38/671:18-672:3; A26152/686:1-15 (Myrdal); A39484-89.) The data confirmed Dey’s own testing, which found that at pH 5, buffer concentration and oxygen did not noticeably affect stability. (A178/10:23-26; A33411-14; A26163/697:7-21; A26164/698:14-18; A26194/728:3-14 (Myrdal).)

4. Ingredients and Proportions Are Taught by the Prior Art

Water, the solvent in Gao and Murakami, is a polar, protic solvent. (A1079/20:1-6; A304/38:1-16; A26276-77/810:24-811:5 (Hendeles).) Gao and Murakami both include sodium chloride (a tonicity adjusting agent) and citrate buffer, at a pH of 5.0 (Gao) or 4.0 – 6.0 (Murakami). (A1079/20:1-6; A304/38:1-16; A25928-29/467:7-468:5; A25933-36/472:23-475:4 (Myrdal); A26275-79/809:1-813:6 (Hendeles).) The ionic strength of the compositions in Gao and Murakami is about 0.16. (A1079/20:1-6; A304/38:1-16; A25641-42/183:17-184:11 (Chaudry); A25799/341:8-25 (Barnes); A26294-95/828:15-829:1 (Hendeles).)

The citrate buffer concentration in Murakami is about 5 mM. (A25946-47/485:21-486:13 (Myrdal); A304/38:1-16; A25799/341:8-22 (Barnes).) The art taught a pH of about 5 for aqueous formoterol solutions, and a POSA would have been motivated to use a buffer that maintained that pH. (A1079/20:1-6; A304/38:1-16; A25589-90/139:19-140:3 (Chaudry); A25766/308:5-19 (Barnes); A25911-12/450:8-451:23 (Myrdal); A435.) Citrate buffers were commonly used, and the prior art disclosed concentration ranges that included about 20 mM. (A456/3:48-59.) Determining the optimum buffer concentration was a routine procedure in formulation development. (A25576/126:4-7 (Chaudry); A25935/474:10-22 (Myrdal); A26939-40/1454:19-1455:17 (Hastedt).) The

specific buffer concentration was an insubstantial difference and was a design choice.

Dey's patents teach no critical difference between the claimed 20 mM buffer concentration and a 5 mM buffer concentration at a pH of about 5. Dey's patents acknowledge that "no noticeable differences in [the stability] rate constant were observed in the pH region of about 4.5 to about 5.5 with increasing the buffer concentration from 5 mM to 20 mM." (A178/10:23-26.) Simple concentration variations do not yield a patentable difference. *See Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989).

5. Formoterol Salts and Enantiomers Are Taught by the Prior Art

Claims 104 and 116 of the '344 patent and claim 160 of the '953 patent require formoterol to be provided as a (i) racemic mixture of enantiomers or stereoisomers of formoterol or a salt or hydrate thereof, (ii) fumarate or tartrate salt of such a racemic mixture, and/or (iii) formoterol fumarate dihydrate. The Gao formulation includes the tartrate salt of arformoterol. (A26277-78/811:19-812:3; A1079/20:1-3.) Murakami discloses that the bronchodilator compounds may be present as salts, including fumarate salts, and the active ingredient in Murakami Example 34 is the fumarate salt of a formoterol analog, which, like formoterol, is a mixture of enantiomers. (A26274/808:5-13 (Hendeles); A287/4:42-46; A289/7:57-64; A304/38:1-16.) The limitations in claims 104 and 116 were well-

known features of formoterol fumarate dihydrate used in commercially available racemic Foradil[®]. (A26306/840:4-16.)

6. Unit Dosage and Packaging Are Taught by the Prior Art

Claims 65, 104, and 116 of the '344 patent and claims 160 and 163 of the '953 patent recite or depend from a claim that requires a composition “formulated for single dosage administration” or provided in a “single use container,” a “unit dosage form,” a “single dosage form”, and/or a volume of “about 2 mL.” Unit dose formulations for inhalation drug products were well known in the art.

Murakami teaches sterilizing and adding solution to 1-ml ampoules, which are sterile unit dosage forms. (A26403-04/930:9-931:16 (Hendeles); A304/38:1-16.) Prior art inhalation solutions were formulated for single dosage administration and packaged in sterile unit dose vials (e.g., 2-3 ml) as recommended by the FDA. (A26222-23/756:14-759:23; A26350-63/877:10-890:22; A26375/902:2-13 (Hendeles); A424-29; A463-67; A521-23; A524-27; A528-31; A532-36; A1039-45; A1046-50; A1146-53; A1154-70; A537-43.)

Packaging Gao's inhalation solution was a known solution to the problem of providing a unit dosage form. (A26287-89/821:19-822:8; A26304-05/838:12-839:9 (Hendeles); A1079/20:1-3.) A POSA knew to determine the unit dose volume according to the desired quantity for nebulization, and knew to formulate the volume, as a matter of routine skill. (A25591/141:17-25 (Chaudry);

A26231/765:8-16; A26375/902:2-13 (Hendeles).) The volumes, doses, and containers required by the claims do not render the claims patentable.

Claim 65's label limitation does not present a patentable distinction over the art. Dey did not invent labels and is claiming the FDA-required label. 21 U.S.C. §§352(a)-(f). FDA-required labeling cannot render the obvious composition patentable, as "[t]he instructions in no way function with the drug to create a new, unobvious product." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1064-65 (Fed. Cir. 2010).

7. The Method Claims Are Not Patentable

The '953 patent method claims require the expected result of a method for treating bronchoconstrictive disorders by administering, by nebulizer, compositions including all the elements of asserted '344 patent claims. Since the compositions are obvious, using them as expected is also obvious. *See Enzo Biochem*, 424 F.3d at 1285.

8. The District Court Erred in Distinguishing Gao

The District Court distinguished Gao by concluding that Dey disclaimed concentrations of 139 µg/ml of formoterol as the free base during reexamination. (A34-35.) The Court was wrong. Dey did not make the requisite "clear and unmistakable" disclaimer of claim scope required to limit the term "suitable for direct administration." *See Elbex Video, Ltd. v. Sensormatic Elecs. Corp.*, 508

F.3d 1366, 1371-72 (Fed. Cir. 2007). Dey's alleged disclaimers are footnotes from the '344 and '953 reexamination file histories that refer only to certain claims and do not refer to the Asserted Claims generally. (A15618; A15624; A18903; A18910.)

The specifications of the First Patent Family do not disavow concentrations of 139 µg/ml and above for those claims which lack an explicit concentration range, instead revealing that even much higher concentrations are suitable for direct administration. (A177/8:46-67.) The specifications describe formoterol concentrations as high as about 2,000 µg/ml. (A177/8:46-67.) Dr. Chaudry also admitted that the '344 and '953 patents were intended to cover high concentration, low volume (0.5 ml) formulations suitable for direct administration by nebulization, not only 2-ml formulations, as in Perforomist[®]. (A13895-96/85:3-90:13.)

The District Court also erred in concluding that a free base concentration of 139 µg/ml of formoterol is not "suitable for direct administration" because it is "'too high' for the long term treatment of COPD." (A34-35.) None of the Asserted Claims include a limitation concerning the duration of treatment. "[L]ong-term treatment of COPD" is irrelevant. However, to the extent the District Court construed the claims as pertaining to "long term treatment of COPD," this construction is erroneous, and it is entitled to no deference on appeal.

See Lighting Ballast, 744 F.3d at 1292.

9. The District Court Erred in Finding Murakami Not Enabled

Murakami enables a POSA to practice the alleged inventions of the Asserted Claims without undue experimentation. As stated in *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006), a prior art reference need only be “enabling in the sense that it describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention.” Murakami disclosed example formulations in which any of the three preferred bronchodilator compounds could be used for an inhalation solution by nebulization. (A25928-32/467:4-471:20 (Myrdal); A26246/780:6-19 (Hendeles); A289/7:65-8:3.) The District Court overlooked Dr. Hendeles’ testimony that the formulation of Murakami Example 34 could be used as a nebulizer solution, based on his experience nebulizing injectable formulations. (A26246/780:6-19 (Hendeles).)

As of the critical date, a POSA also would have known that formoterol fumarate (e.g., Foradil[®]) was useful to treat COPD and that formoterol was the only Murakami compound developed commercially. (A25932/471:11-20 (Myrdal).) By March 2000, a POSA would have known that formoterol was the primary Murakami compound of interest, and that the Murakami examples pertained not only to the active example compound, but also to formoterol. (A25928-32/467:7-471:20 (Myrdal).)

D. The Second Patent Family Asserted Claims Are Invalid As Obvious

The Second Patent Family Asserted Claims include many of the same elements as the First Patent Family Asserted Claims. The teachings of Gao and Murakami also apply to the Second Patent Family Asserted Claims. Puigbó and Gavin also teach propellant-free, aqueous compositions comprising formoterol in saline solution, at about pH 5.5. (A1056; A1687/1:1-11; A1697; A25762-63/304:22-305:4 (Barnes); A26365-67/892:22-894:5 (Hendeles).) Using formoterol as the active ingredient in a composition according to Murakami Example 34 would have been obvious in view of Gao, Puigbó, Gavin, and Foradil[®]. (See A25928-32/467:7-471:20; A25947-48/486:14-487:1 (Myrdal).)

The Second Patent Family Asserted Claims require the following elements:

- sterile unit dose comprising about 0.1 ml to about 3.0 ml, or about 2.0 ml;
- formoterol concentration of from about 0.08 µg/ml to about 34 µg/ml, or about 26 µg/ml, or about 43 µg/ml, based on the free base;
- packaged in pharmaceutical packaging material or in a vial overwrapped with a laminate

Murakami discloses that the composition is sterilized and packaged in 1-ml ampoules, which are unit doses in pharmaceutical packaging material.

(A26244/778:18-779:13 (Hendeles); A304/38:1-16.) 2-3 ml unit dose vials were commonly used prior to the critical date. (A25764/306:9-15 (Barnes); A26218-26/752:18-760:15 (Hendeles).)

Puigbó taught diluting Foradil® dry powder in 2 ml, 0.9% sterile saline solution and administering the solution by nebulization to treat bronchoconstriction. (A26366-67/893:23-894:5 (Hendeles); A1056.) Gavin disclosed a buffered aqueous nebulizer formulation comprising 12 µg formoterol fumarate in 2 ml aqueous solution. (A26365-66/892:22-893:20; A1697.)

The prior art reveals that a POSA would have been motivated to make a formoterol inhalation solution in a unit dose in pharmaceutical packaging material for administration by nebulization at a formoterol concentration in the claimed range of from about 0.08 µg/ml to about 26 µg/ml. A POSA would have known to overwrap the unit dose to protect it from light and would have expected the solution to be useful to administer to patients without dilution.

The Court found that Gao, Redmon and Puigbo “taught against the elements that Dey used to create its invention” because these references teach keeping formoterol dry until just prior to use. (A58-59.) The Court misapplied the law of “teaching away.” Presenting an alternative, as these references do, does not “teach away” from what is already known in the art. *See In re Berg*, 320 F.3d 1310, 1316 (Fed. Cir. 2003) (citing *In re Beattie*, 974 F.2d 1309, 1312-13 (Fed. Cir. 1992)); *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (“A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.”). A teaching that dry formoterol

“may be optimal or standard does not criticize, discredit or otherwise discourage investigation into other compositions.” *Galderma Labs. L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

The asserted claims of the ’362 and ’645 patents are directed to compositions and methods that include known formoterol dosage strengths, known buffer concentrations, known volumes, and known packaging. These elements are, at most, merely minor, insignificant variants of the compositions disclosed in Gao, and/or Puigbó, and/or Gavin, and/or taught by Murakami as described above. *See Merck*, 874 F.2d at 809. The asserted claims of the ’362 and ’645 patents are invalid under 35 U.S.C. §103 as obvious to a POSA in view of this art, alone or in combination.

E. There Is No Evidence the Patent Office Fully Considered the Prior Art

The District Court stated that some publications relied on by Teva were “considered” by the USPTO during prosecution. (A19-21; A25.) Whether the references were considered by the USPTO is of no consequence, as “there is no heightened burden of proof when a reference was previously considered by the PTO.” *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) (citing *Microsoft Corp. v. i4i Ltd. P’ship*, 131 S. Ct. 2238, 2250 (2011)). However, when the USPTO “did not have all material facts before it, its considered judgment may lose significant force.” *i4i*, 131 S. Ct. at 2251 (citing *KSR Int’l*, 550 U.S. at

427). Here, the USPTO did not have all the material facts before it, at least because the Sepracor Lots were not considered when the Patents-in-Suit were prosecuted. (A169-73; A213-16; A255-58; A271-74.) The Sepracor Lots were also not considered in the reexaminations of the First Family patents because reexamination is limited to prior art patents and printed publications. 35 U.S.C. §§301, 302. Further, the USPTO did not consider the near-simultaneous development of formoterol inhalation solution formulations by separate groups of scientists such as Sepracor/Dey.

F. Objective Considerations Are Not Compelling

Objective considerations are to be considered in the obviousness analysis. *Graham*, 383 U.S. at 17-18. However, here, the differences between the claimed invention and the prior art are so minor that objective evidence of nonobviousness is not sufficiently compelling to support the patentability of any Asserted Claim. *See B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1583 (Fed. Cir. 1996).

To rely on objective considerations, their proponent, Dey, must establish “a nexus between the evidence and the merits of the *claimed invention*.” *In re Kao*, 639 F.3d at 1068 (quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). Thus, “[w]here the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no

nexus to the merits of the claimed invention.” *In re Kao*, 639 F.3d at 1068; *see also J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) (commercial success must be due to the merits of the claimed invention beyond what was readily available in the prior art).

1. Dey Did Not Establish a Nexus Between Perforomist® Sales and the Asserted Claims

The District Court erred as a matter of law in holding Dey’s allegations of commercial success relevant to obviousness, because Dey failed to show a nexus between alleged secondary considerations and the Asserted Claims, as it must. *See Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392-1393 (Fed. Cir. 1988).

To meet its burden, Dey had to demonstrate, in part, that the alleged commercial success was attributable to a feature not readily available in the prior art. *J.T. Eaton*, 106 F.3d at 1571; *see also In re Kao*, 639 F.3d at 1068. Dey has not done so. The features of the Asserted Claims were readily available in the prior art and are not pertinent to the analysis. *Ormco Corp. v. Align Tech. Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). Aqueous inhalation solutions of formoterol, administered via nebulization, and stored under refrigeration to prolong stability, were well-known. The stability defined in the Asserted Claims is an inherent property of prior art solutions.

2. The Alleged Inventions Did Not Meet a Long-Felt Need

The District Court emphasized that “many COPD patients lack the ability to effectively use DPIs, which require strength and cognitive skills to coordinate inhalation with manipulation of the devices.” (A68.) This supposedly gave rise to an unmet need for a non-DPI solution of formoterol in 2001. (A68-69.) The Court did not point to any novel feature of the Asserted Claims that met this alleged need. This was an error of law as the nexus requirement applies to all secondary considerations. *In re Kao*, 639 F.3d at 1068.

The District Court also failed to acknowledge that the alleged long-felt need was met by 2001. In 1999, Serevent[®], a long-acting bronchodilator, was available as an MDI that could be administered using a valved holding chamber (A26309/843:1-10; A26311-12/845:15-846:14 (Hendeles)), to produce the same therapeutic effect as formoterol. (A26311-12/845:15-846:14 (Hendeles).) Dey’s expert acknowledged that “Serevent[®] is very similar to formoterol in its duration of action” (A25740/282:2-5 (Barnes)), and agreed that with valved chambers, “[n]ormally, the patient would press the canister into the chamber and then breathe from the valve into the lung. So, in other words, *it gets around the problem of coordination between activating the device and inhaling.*” (A25855/397:13-19, emphasis added.)

The District Court also found that Perforomist[®] must have met a long felt need because doctors prescribe it and insurance companies include it in formularies. (A69.) This finding is legally flawed because it analyzes long-felt-need in the wrong time period – after Perforomist[®] entered the market – rather than the filing date of Dey’s patents. One must “look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need.” *See Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). The evidence does not establish that at the time of the invention there was an unmet need for a formoterol inhalation solution.

3. Copying Is Not Probative of Obviousness

The District Court erred as a matter of law in relying on evidence of “copying” by Teva to support the patentability of the Asserted Claims in this Hatch-Waxman case. (A70.) The Court penalized Teva for doing exactly what the Hatch-Waxman act encourages. *See Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (“[E]vidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval.”). Even before *Bayer*, evidence of copying was not compelling even if the generic drug company reverse-engineered the brand name product. *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 458 (D. Del. 2010), *aff’d in relevant part, rev’d in part on other grounds*,

Santarus, Inc. v. Par Pharm., 694 F.3d 1344 (Fed. Cir. 2012). Contrary to the Court’s characterization (A71), Teva prepared a formulation based on the reference listed drug per FDA requirements. (A13833/21:08-22:03.) The regulations encourage generic manufacturers to copy the entire drug product – not only the active ingredient. The FDA waives evidentiary requirements regarding the bioequivalence of a nebulized generic product, 21 C.F.R. §320.22(b)(3), when there are no significant changes to the *inactive ingredients* in the formulation. Teva’s efforts to comply with the regulatory requirements are not a “secondary consideration” supporting the validity of the claims.

CONCLUSION

Teva respectfully requests this Court to grant the following relief: (i) reverse the District Court, and hold that “pharmaceutical composition” must be “stable”; (ii) reverse the District Court’s judgment on infringement; (iii) reverse the District Court’s judgment that the Asserted Claims are not invalid, and hold the Asserted Claims invalid under §§102 and 103; (iv) reverse the District Court and hold that the Sepracor Lots were “on sale,” remanding, if necessary, for further consideration of the invalidity of the Asserted Claims; and (v) dissolve the injunction.

Respectfully submitted,

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*Dey L.P., Now Known as Mylan Specialty, L.P., and Dey, Inc. v.
Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd.,
and Teva Pharmaceuticals USA, Inc.*

Case No. 2014-1434

Addendum

1. March 21, 2014 Judgment,
Dey, L.P. et al. v. Teva Parenteral Medicines, Inc. et al.,
Case No. 1:09-cv-00087 (IMK) (N.D.W. Va.).....A1-A76
2. June 17, 2011 Memorandum Opinion and Order,
Dey, L.P. et al. v. Teva Parenteral Medicines, Inc. et al.,
Case No. 1:09-cv-00087 (IMK) (N.D.W. Va.).....A77-A120
3. July 17, 2013 Order,
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4. July 29, 2013 Stipulation and Order,
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Case No. 1:09-cv-00087 (IMK) (N.D.W. Va.).....A166-A168
5. United States Patent No. 6,667,344.....A169-A211
6. United States Patent No. 6,814,953.....A212-A253
7. United States Patent No. 7,348,362.....A254-A269
8. United States Patent No. 7,462,645.....A270-A284

Addendum 1

March 21, 2014 Judgment,
Dey, L.P. et al. v. Teva Parenteral Medicines, Inc. et al.,
Case No. 1:09-cv-00087 (IMK) (N.D.W. Va.)

A1-A76

*Dey L.P., Now Known as Mylan Specialty, L.P., and Dey, Inc. v.
Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd.,
and Teva Pharmaceuticals USA, Inc.
Case No. 2014-1434*

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

DEY, L. P. and DEY, INC.,

Plaintiffs,

v. // CIVIL ACTION NO. 1:09CV87
(Judge Keeley)

TEVA PARENTERAL MEDICINES, INC.,
TEVA PHARMACEUTICALS USA, INC., and
TEVA PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants.

FINDINGS OF FACT AND CONCLUSIONS OF LAW GRANTING
JUDGMENT IN FAVOR OF THE PLAINTIFFS, DEY L.P. AND DEY, INC.

I. INTRODUCTION

The plaintiffs, Dey, L.P. and Dey Inc. (collectively "Dey"), have asserted eight causes of action against the defendants, Teva Parenteral Medicines, Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceutical Industries, Ltd. (collectively "Teva") regarding Teva's infringement of four of Dey's patents associated with the drug Perforomist[®].¹ (Dkt. No. 1). On July 17, 2013, the Court granted partial summary judgment in favor of Dey on the issue of infringement, finding that the product described in Teva's Abbreviated New Drug Application ("ANDA") infringes claims 1 and 65 of the 6,667,344 Patent ("the '344 Patent"). (Dkt. No. 211). Teva

¹These four patents include: 6,667,344 ("the '344 Patent"), 6,814,953 ("the '953 Patent"), 7,348,362 ("the '362 Patent"), and 7,462,645 ("the '645 Patent") (collectively, the "patents-in-suit").

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contends that infringement is warranted in this instance because the patents-in-suit are invalid on a number of grounds.

Between July 29, 2013 and August 6, 2013, the Court conducted a bench trial on Teva's invalidity defenses of anticipation, obviousness, and enablement. In lieu of closing arguments, the parties submitted post-trial memoranda. All briefing concluded on October 29, 2013.

On the basis of the record and the applicable law, the Court issues the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52,² and concludes that Teva has failed to meet its burden of proving by clear and convincing evidence the invalidity of the patents-in-suit.

II. THE RECORD AND RELEVANT PROCEEDINGS

A. PROCEDURAL HISTORY

In a letter dated May 12, 2009, Teva, the world's largest manufacturer of generic drugs, notified Dey that it had filed an ANDA seeking United States Food and Drug Administration ("FDA") approval to market a generic version of Perforomist®. Pursuant to

²To the extent that any findings of fact may be deemed conclusions of law, they shall also be considered conclusions of law; to the extent that any conclusions of law may be deemed findings of fact, they shall also be considered findings of fact. Miller v. Fenton, 474 U.S. 104, 113-14, 106 S.Ct. 445, 88 L.Ed.2d 405 (1985).

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21 U.S.C. § 355(j) (2) (A) (vii) (IV), Teva also filed a Paragraph IV certification with the FDA, alleging that the four patents issued to Dey for Perforomist® are invalid, unenforceable, and not infringed by Teva's manufacture or sale of the proposed generic drug product.

Dey responded to Teva's ANDA by filing this action pursuant to the Hatch-Waxman Act, which "gives a drug patent owner the right to bring an action for infringement upon the filing of a paragraph IV certification." Bristol-Myers Squibb Co. v. Royce Laboratories, Inc., 69 F.3d 1130, 1135 (Fed. Cir. 1995) (citing 35 U.S.C. § 271(e) (2) (A)). When a branded manufacturer files suit pursuant to that right within 45 days of notice of the Paragraph IV certification, as was the case here,³ the litigation automatically stays the generic's entry to the market. 21 U.S.C. § 355(j) (5) (B) (iii).

The purpose of the Hatch Waxman Act, then, is to shift risks between the patent holder and generic manufacturer, allowing the generic manufacturer to challenge the validity of a patent without risking damages from infringement. More importantly, for purposes of this trial, this structure allows the parties to try the dueling

³Dey filed suit 42 days after receiving notice of Teva's ANDA.

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issues of patent infringement and invalidity in one action. Ark. Carpenters Health & Welfare Fund v. Bayer AG, 544 F.3d 1323, 1338 (Fed. Cir. 2008).

B. Claim Construction

Following extensive briefing and a claim construction hearing, the Court issued a Memorandum Opinion and Order Construing Patent Claims, (dkt. no. 99), which construed the patent claims at issue to the extent the parties disputed the meaning of claim terms. For the purposes of this trial, that Memorandum Opinion and Order “define[s] the invention to which the patentee is entitled the right to exclude.” Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005).

C. Infringement

On September 21, 2012, Dey moved for partial summary judgment on the issue of infringement. (Dkt. No. 159). Following a hearing, the Court granted the motion, (dkt. no 211), which Teva did not appeal. Thus, the only issue remaining is whether Teva has established, by clear and convincing evidence, that the patents-in-suit are invalid.

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D. Expert and Other Witnesses**1. Dr. Peter Barnes**

Dr. Peter Barnes, a witness proffered by Dey, is an expert in the field of respiratory disease research. He received a BM, BCh (MD equivalent) degree from the University of Oxford in 1972. He also received a Medical Research degree and later a Doctorate in Science from the University of Oxford.

Dr. Barnes is currently President-Elect of the European Respiratory Society. Since 1987, he has been Professor of Thoracic Medicine at the National Heart and Lung Institute, Head of Respiratory Medicine at Imperial College, London, and honorary Consultant Physician at Royal Brompton Hospital.

Since 1978, Dr. Barnes has focused his research on cellular and molecular mechanisms of asthma and COPD. He has published over 1,000 articles in peer reviewed journals and has written, edited or co-edited over 1000 articles on the topics of asthma, COPD and pulmonary pharmacology. In addition to his research work and medical practice, Dr. Barnes has consulted with several pharmaceutical companies involved in the development and marketing of drugs for the treatment of asthma and COPD. (Dkt. No. 201).

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2. Dr. Jayne Hastedt

Dr. Jayne Hastedt testified for Dey as an expert in the field of pharmaceutical compositions. Dr. Hastedt received an Associate in Science degree in Chemical Engineering from Waterbury State Technical College in 1980, and a Bachelor of Arts degree in Biochemistry from Western Connecticut State University. She also received a Master in Science and later a Ph.D. in Pharmaceutics from the University of Wisconsin-Madison School of Pharmacy.

Dr. Hastedt is currently CEO and Co-Founder of JDP Pharma Consulting, LLC. She also serves as an Adjunct Professor at the Thomas J. Long School of Pharmacy and Health Sciences at the University of the Pacific. Previously, she worked as a Research Investigator and Researching Leader in the Pharmaceutics Department at Glaxo Research Institute. She also held positions as Product Development Manager, Director of ChemPharm Management, and Senior Director for West Coast ChemPharm while working for ALZA Corporation, a Johnson & Johnson Company.

Dr. Hastedt has lectured on dissolution and diffusion at the University of North Carolina School of Pharmacy and California Polytechnic State University. She has also served as a reviewer for various pharmaceutical journals.

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3. Dr. Imtiaz Chaudry

Dr. Imtiaz Chaudry is one of the named inventors on the patents-in-suit. He received his Master in Science degree from the Philadelphia College of Pharmacy and Science and his Ph.D. in Pharmacy from St. John's University. He is also a licensed pharmacist.

Dr. Chaudry is currently Senior Vice President of Scientific Affairs at Dey, where he leads a research group charged with developing new drug compounds for the company's future branded products line. Dr. Chaudry has been employed by Dey since 1999. Prior to joining Dey, he was Vice President of Pharmaceutical Development at Schering-Plough Research Institute, where he worked for over two decades.

Dr. Chaudry has published over 20 articles in peer reviewed scientific journals. He has served on the University of Kansas, Drug Delivery Center, Scientific Advisory Board, and was a member of the Board of Governors of the Controlled Release Society for Bioactive Materials. (Dkt. No. 201).

4. Dr. Steve Wald

Dr. Steve Wald is a former employee of Sepracor, Inc. ("Sepracor"), where he worked from 1985-2009. Dr. Wald received a

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Master in Science degree from the University of California, Berkeley, and a Bachelor of Science degree in Chemical Engineering from Cornell University.

While at Sepracor, Dr. Wald served as Senior Vice President of Chemistry & Pharmaceutical Sciences and also of Commercial and Technical Operations. Notably, for purposes of the scope of this litigation, Dr. Wald oversaw the development of the product Brovana[®], including Sepracor's Transactions with Automated Liquid Packaging ("ALP"), during his time at Sepracor.

5. Dr. Leslie Hendeles

Dr. Leslie Hendeles is an expert witness proffered by Teva in the field of inhalation solutions. Dr. Hendeles received a Doctor of Pharmacy degree from the University of Southern California in 1969. He currently is a professor in the College of Pharmacy and in the Department of Pediatrics at the University of Florida. He also is a practicing Clinical Pharmacist at the University of Florida's Pediatric Pulmonary Clinic.

Dr. Hendeles has taught, researched, and made recommendations to physicians about inhalation solutions for over thirty years. He has also conducted clinical trials and published extensively regarding pharmaceutical formulations for bronchoconstriction. He is a consultant to the Pulmonary/Allergy Drugs Division of the

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Center for Drug Evaluation and Research at the U.S. Food and Drug Administration where he assists in evaluating the safety and effectiveness of drugs used to treat pulmonary and allergic diseases.

In the last five years, Dr. Hendeles has conducted at least ten clinical trials relating to the treatment of asthma and cystic fibrosis. He is currently conducting a study to determine the bioequivalence of formoterol delivered by novalizer and aerolizer devices. (Dkt. No. 201).

6. Dr. Paul B. Myrdal

Dr. Paul B. Myrdal was proffered by Teva as an expert in the field of inhalation drug delivery techniques and technologies. He received a Bachelor of Science degree in Molecular and Cellular Biology from the University of Arizona in 1989, and a Ph.D. in Pharmaceutical Chemistry from the University of Arizona in 1994. Currently, he is an Associate Professor in Pharmaceutics at the University of Arizona. Prior to that, from 2000-2006, he served as an Assistant Professor in Pharmaceutics at that university.

Dr. Myrdal's research at Arizona includes the understanding of the chemistry and product performance of HFA-based metered dose inhalers, the development of topical formulations for skin cancer, formulation of poorly soluble compounds and evaluation of oral

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bioavailability, preclinical testing of nebulized agents for the chemoprevention of lung cancer, and traditional preformulation and formulation activities.

From 1995-2000, Dr. Myrdal worked at 3M Pharmaceuticals, where he was involved in the development of conventional and novel inhalation delivery techniques and the preformulation and formulation of new chemical entities for pulmonary delivery. He has also served as a consultant for the pharmaceutical industry on various preformulation, formulation, and related drug delivery techniques.

III. FINDINGS OF FACT

A. Dey's Development of Perforomist

Through the process of developing Perforomist®, Dey invented, patented, and sold a unique inhalation solution for the treatment of chronic obstructive pulmonary disease ("COPD"). Perforomist® embodies the attributes of long-term stability and a ready to use unit dose of a long-acting beta agonist ("LABA") suitable for nebulization. To date, Perforomist® and a formerly infringing but now licensed competitor, Brovana®, are the only LABAs approved in the United States for treatment of COPD by nebulization. (Tr.944:8-17 (Hendeles).)

Dey's goal in developing Perforomist was to become "a leader in the area of nebulization. [Dey's] strong view was that there [was] an

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unmet need as far as bringing new medications in COPD for nebulization." (Tr. 47:22-25 (Chaudry).) Dey recognized that a significant segment of the COPD population, namely elderly patients, had trouble using the dry powder inhaler ("DPI") and metered dose inhaler ("MDI") treatments then available, as these required coordinating inhalation with manipulation—precisely the abilities many elderly patients lacked.

Dey came to identify formoterol, a LABA, as a "good opportunity for developing [a] nebulization product." (Tr. 48:20-49:3 (Chaudry), 254:22-255:3 (Barnes).) Formoterol was first discovered as an effective bronchodilator, and patented (U.S. Patent No. 3,994,974 ("Murakami")) in the 1970s. (Tr. 54:2-5 (Chaudry).) Formoterol quickly became widely used outside the United States. At the time Dey began its development program in 1999, however, "there [were] no formoterol product[s] for nebulization anywhere in the world," and no formoterol products whatsoever in the United States. (TX 269; Tr. 57:14-19 (Chaudry); TX 1, 7:37-46.)

From the start, Dey's scientists faced the challenge of the instability of formoterol in aqueous solutions. Two of those scientists, Drs. Partha Banerjee and Imtiaz Chaudry, leaders of the formoterol inhalation solution project at Dey, knew that formoterol was "prone to degradation by hydrolysis." (Tr. 58:5-15, 146:20-147:1

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(Chaudry).) A search of the leading formoterol literature at the time confirmed formoterol's aqueous instability. (Tr. 58:16-25, 60:23-61:7, 78:25-79:7 (Chaudry).)

For example, U.S. Patent No. 6,040,344 ("Gao") taught that "because of the problematic stability" of formoterol "in aqueous solutions," a formulation of formoterol in "citrate buffered saline, buffered to pH 5 . . . is not attractive for long term storage." (TX 15, 20:1-6.) Dey scientists understood from this that "formoterol in an aqueous[,] or water-based[,] solution is not adapt[ed] or appropriate for long-term storage." (Tr. 66:25-67:10 (Chaudry).)

The Gao Patent also referred to U.S. Provisional Application 60/061,363 (later issued as U.S. Patent No. 6,161,536 ("Redmon")), which stated that formoterol is "not sufficiently stable in an aqueous environment to provide a practical shelf life for the aqueous formulation" and suggested instead to "make up the [formoterol] solution immediately before use." (TX 17, 1:53-55, 62-64; TX 612 (Redmon PCT publication).) The Dey scientists thus learned that it would not be feasible to "mix the [aqueous] solution and the [formoterol] dry-powder and then keep it in that form for periods of weeks or months before using it." (Tr. 69:6-11 (Chaudry).)

According to U.S. Patent No. 6,150,418 ("Hochrainer"), "formoterol cannot be stored in a sufficiently stable manner in a

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solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time." (TX 13, 1:30-35.) On the contrary, Hochrainer taught an "active substance concentrate" that could be stored and then "converted by dilution into a therapeutically effective formulation" to be used "within a few minutes or possibly a few seconds." (TX 13, 1: 62-67, 5:21-26.) From this, the Dey team came to understand that when formoterol is present in water, "a very highly concentrated solution or a suspension" is necessary to "have reasonable stability for a longer storage." (Tr. 69:24-70:8 (Chaudry).)

Due to the technical challenges they faced, Drs. Chaudry and Banerjee "were highly skeptical that a stable, aqueous-based nebulized formulation, . . . c[ould] be developed." (Tr. 78:25-79:3; 82:9-12, 189:11-14 (Chaudry).) They were not aware of any "ready fixes" that would result in a stable, ready-to-use aqueous solution. (Tr. 79:8-12 (Chaudry).) Furthermore, they were not confident that, even if they could identify a solution composition that would maximize formoterol's stability, it would have sufficient stability to be use effectively. (Tr. 89:2-4, 90:13-21, 91:2-16, 93:21-25 (Chaudry).)

In August 1999, Dey began to test "the amount of formoterol in a solution and also be able to test the breakdown products" of

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formoterol (Tr. 83:7-14, 85:23-25 (Chaudry)). The Dey team used these test results to generate pH-solubility and stability data for formoterol. (TX 61) They determined the solubility at pH 3, 4, 5, and 7 (TX 254), which surprisingly was "more than adequate solubility in water to develop a nebulization product." (Tr. 96:1-4, 10-20 (Chaudry).) Dey also discovered that formoterol was most stable at pH 5. (TX 254; Tr. 98:15-17, 99:17-23 (Chaudry); TX 293.1(discussing later experiments confirming maximum stability between pH 4.8 and 5.1).)

Based on these experiments, Dr. Stephan Pham, a scientist who joined Dey in 2000 (Tr. 99:3-10 (Chaudry)), determined that formoterol degradation was likely affected by solution pH, buffer concentration, and ionic strength, but the "extent of the individual effects" remained to be determined. (TX 69). The team also "knew by [September 2000] what other ingredients [they] would like to use and [had in] mind a core formulation" for further refinement. (Tr. 100:2-13 (Chaudry).) Dr. Pham focused on formulations containing 5, 10, and 20 mM citrate, acetate, and phosphate buffers, to control pH, and sodium chloride, to control ionic strength. (TX 80).

Dr. Pham's experiments illustrated that "buffer concentration had no appreciable effect on [formoterol stability] in pH region 4.6 - 5.6," but did have a significant effect within other pH ranges. (TX

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293.1; TX 80; Tr. 103:5-8 (Chaudry).) The effect of buffer concentration was a subject other researchers had failed to address. Ultimately, Dey selected a buffer concentration of 20 mM to ensure that the pH did not drift upward over time, as had occurred with lower buffer concentrations. (TX 293.1; Tr. 103:21-104:24 (Chaudry).) Dr. Pham also determined that the sodium chloride concentration necessary for isotonicity "would have a minimal effect on the [formoterol fumarate] stability" in a buffered pH 5 solution. (TX 293.1; TX 80; Tr. 105:11-22 (Chaudry).)

Dr. Pham also tested the stability of a version of Dey's "core formulation" (5 mM acetate buffer at pH 5.2, with an ionic strength of 0.05), and employed Arrhenius kinetics to project its shelf life. (See, TX 80). Contrary to expectations, by November, 2000 Dey had discovered that this formulation had an estimated shelf life (90% of the initial formoterol remaining) of about six years at 5°C and about eight months at 25°C (approximately room temperature). (TX 72; TX 293.1).

After confirming the stability of the core formulation, Dey then began to refine it. The scientists chose a formulation containing a citrate at pH 5 (TX 80) and, ultimately, a 20 mM citrate buffer concentration. (Tr. 112:3-14 (Chaudry).) Later, based on clinical studies conducted in 2003, Dey chose a formoterol dose that was

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similar to the standard dose of Foradil® (Tr. 112:15-25, 164:14-22 (Chaudry)), a formoterol DPI product approved by the FDA in February of 2001. (Tr. 55:16-18 (Chaudry); Tr. 841:17-19 (Hendeles).)

Dey had never considered refrigeration, by itself, to be a viable strategy, and its tests confirmed this suspicion. (TX 12; Tr. 117:18-119:5, 198:2-10 (Chaudry).) Dey's testing of formoterol in water showed that, after six months of storage at 5°C, only 91% of the initial formoterol remained. (TX 12; Tr. 117:18-119:5 (Chaudry) (extrapolating to 18 to 20% degradation after one year).) After six months at room temperature, only 80% formoterol remained. (TX 12; Tr. 117:18-119:5 (Chaudry) (interpolating to 3 to 4% degradation after one month).) This was not sufficient for Dey; it wanted to create a formoterol product with "a shelf life of 24 months at [a] long-term storage condition, including 3 months at room temperature after dispensing" from the pharmacy. (TX 293.1; Tr. 195:13- 20 (Chaudry).) Formoterol in water satisfied neither of these requirements. After a year at 5°C (predicted 18-20% degradation), plus a month at room temperature (3-4% degradation), formoterol in water would degrade at least 20 percent (Tr. 117:18-119:5, 198:2-10 (Chaudry)), if not more. Reflecting long-term storage needs, Dey's patents require that at least 80% formoterol remain after consecutive storage conditions of

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"one year at 5°C refrigeration and one month at room temperature."
(Tr. 118:4-8 (Chaudry); e.g., TX 1, claim 3.)

The stable, ready-to-use formoterol inhalation solution that Dey invented is now marketed as Perforomist®. Perforomist® is indicated for "[l]ong term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction" in patients with COPD. (TX 49; Tr. 1197:2-9 (Graybill); Tr. 1007:21-24 (Hendele).) Each vial of Perforomist® contains 2mL of 10 µg/mL formoterol fumarate in "an isotonic, sterile aqueous solution containing sodium chloride, pH adjusted to 5.0 with citric acid and sodium citrate." (TX 49). The drug is refrigerated at a temperature between 2-8°C before being sold to the consumer. (TX 49; Tr. 154:1-6; 163:9-15 (Chaundry).) Once sold, it is expected that Perforomist® may be successfully stored at room temperature (25°C) for up to three months. Id.

B. The Patents-In-Suit

The parties have stipulated⁴ that the proposed generic product described in Teva's ANDA infringes four of Dey's patents. (TX 871). The first two patents, the '344 and '953 Patents, entitled

⁴The stipulation is a result of Teva's failure to appeal from the Court's July 17, 2013 partial summary judgment ruling, in which the Court held that Teva's ANDA infringes the patents-in-suit.

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"Bronchodilating Compositions and Methods" (the "First Family" patents), derive from provisional U.S. patent application 60/284,606 and share essentially identical specifications. The '362 and '645 Patents, entitled "Bronchodilating Beta-Agonist Compositions and Methods" (the "Second Family" patents), derive from provisional U.S. patent application 60/486,386. They too share essentially identical specifications that closely resemble those of the First Family patents.

All four patents-in-suit claim aqueous compositions of formoterol that allow the compositions to remain suitable for direct administration by nebulization during long-term storage. They also cover methods for using these compositions to treat broncho-constrictive disorders:

- The '344 Patent claims pharmaceutical compositions of formoterol that are stable during long term storage and suitable for direct administration (TX 1; Tr. 225:25-226:2 (Barnes));
- The '953 Patent claims methods of administering such compositions for the treatment of bronchoconstrictive disorders (TX 4; Tr. 226:3-4 (Barnes));

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- The '362 Patent claims various "unit dose" formulations of formoterol and methods of using the same. (TX 7; Tr. 226:5-6 (Barnes)); and
- The '645 Patent claims methods for treating bronchoconstriction, including COPD, using such "unit dose" formulations of formoterol (TX 9; Tr. 226:7-9 (Barnes)).

Because of terminal disclaimers, all four patents will expire on June 22, 2021. (TX 49).

C. Prosecution of the Patents-In-Suit

During the prosecution of the four patents-in-suit, examiners at the U.S. Patent and Trademark Office ("PTO") considered a number of prior art references (Tr. 232:1-3 (Barnes)), including, but not limited to:

- Murakami (TX 5; TX 8 at DEY-TV0008942; TX 10 at DEYTV0009176);
- Gao (TX 2 at DEY-TV0000141-142; TX 5 at DEY-TV0004549; TX 8 at DEYTV0004814, '8937-940, '943, '974-978, '9032-035, '049-051; TX 10 at DEYTV0009173-174, '177);
- Redmon (TX 2 at DEY-TV0000141-142, '3997; TX 5 at DEY-TV0004479, '550; TX 8 at DEY-TV0009032-035, '049-051; TX 10 at DEY-TV0009177);

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- Hochrainer (TX 2 at DEY-TV0000082, '141-142, '3988-991, '929-939; TX 5 at DEY-TV0004473-479, '550, '735-737, '747-748; TX 8 at DEY-TV0004814, '8937-940, '943, '974-978, '9032-035, '049-051; TX 10 at DEY-TV0009173-74, '177); and
- PCT Publication No. WO 01/78745 ("Gavin," TX 95) (TX 2 at DEY-TV0003999; TX 5 at DEY-TV0004551; TX 8 at DEY-TV0008945; TX 10 at DEY-TV0009179).

The two First Family patents later underwent reexamination, during which the examiner also considered the following references:

- a publication by Whelan et al. ("Whelan," TX 568) (TX 3 at DEY-TV1729971-984, DEY-TV1730194-197, '202-03, '211-213, '687, '1971; TX 6 at DEY-TV1733992-4005, '353-356, '362-363, '375-377, '544, '769); and
- a publication by Puigbó et al. ("Puigbó," TX 625) (TX 3 at DEY-TV1732956; TX 6 at DEY-TV1735005).

After considering these references during Dey's four patent prosecutions and two reexaminations, the PTO issued the four patents-in-suit and confirmed the patentability of the claims of the two First Family patents. (Tr. 947:20-23 (Hendeles).) During reexamination, the examiner provided a "Statement of Reasons for Patentability and/or Confirmation," which set forth the reasons why these references did not pose an obstacle to patentability:

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[T]he prior art of Maesen, Wade, Remington, Gao, Murakami, Whelan, Hochrainer, Redm[o]n, and Lachman fail to teach or fairly suggest either alone or in combination an aqueous solution of formoterol or its derivative in a pharmaceutical composition that is stable during long term storage and is administered by nebulization as claimed. In addition, the instant independent claims require that the pharmaceutical composition of formoterol is at a concentration effective for bronchodilation by nebulization and suitable for direct administration to a subject in need of bronchodilation without propellant and without dilution of the composition (claim 1) or is in a unit dosage form of formoterol (claim 89 and claim 114) or a unit dosage form comprising [R,R]formoterol (claim 118) with a concentration corresponding to about 5 µg/mL to about 50 µg/mL that is administered by nebulization without dilution for bronchodilation. Moreover, the prior art recognized that increasing the concentration of a stable formulation of formoterol would likely preserve or improve stability, but decreasing its concentration was unpredictable, and likely would lead to instability.

(TX 3 at DEY-TV1731971 ('344 Patent); TX 6 at DEY-TV1734769 ('953 Patent; Tr. 233:5-20 (Barnes).)

IV. STANDARD OF LAW

A defendant "in any action involving...infringement of a patent" may plead as an affirmative defense that the asserted patent is invalid. 35 U.S.C. § 282 (b) (2)-3. Because "[a] patent shall be presumed valid," "[t]he burden of establishing invalidity...rest[s] on the party asserting such invalidity." 35 U.S.C. § 282(a). A defendant asserting patent invalidity must establish that the patent is invalid by clear and convincing

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evidence. Microsoft Corp. v. i4i Ltd., 131 S.Ct. 2238, 2242 (2011).

Invalidity may be established under either 35 U.S.C. § 102 or § 103. Section 102 denies the granting of a patent when the invention cannot be considered new in light of the prior art. This situation arises either when the prior art discloses each and every limitation of the claimed invention (§ 102(a) ("anticipation")), or when the invention was subject to a commercial sale more than one year prior to the filing of the patent application (§ 102(b) ("on-sale bar")). Section 103, by contrast, denies patentability if the claimed invention, though new, was nevertheless obvious to a person of ordinary skill in the art (§ 103(a) ("obviousness")).

V. LEGAL ANALYSIS

Teva argues that the patents-in-suit are invalid under the doctrines of anticipation, obviousness, and enablement. First, it contends that the Asserted Claims were anticipated by the Murakami and Gao Patents, as well as Sepracor's transactions with ALP. Next, it argues that the Asserted Claims were obvious in light of the prior art. Finally, it contends that the Asserted Claims fail to enable a person of ordinary skill in the art to practice the invention without undue experimentation. The Court turns now to the application of these doctrines in this case.

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A. Anticipation**1. Standard of Law**

In order for a patentee to obtain a valid patent, its invention must be novel. 35 U.S.C. § 102. "Invalidity based on lack of novelty (often called 'anticipation') requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee." Hoover Grp. Inc. v. Custom Metalcraft Inc., 66 F.3d 299, 302 (Fed. Cir. 1996). A patent thus is invalid for anticipation if "a single prior art reference discloses each and every limitation of the claimed invention." Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003).

A prior art reference will anticipate the patent claim if it either expressly or inherently discloses each claim limitation. Id. at 1379. To establish inherent anticipation, a defendant must prove, by clear and convincing evidence, that a claim limitation not disclosed by the anticipating reference will still be present when the prior art is practiced as taught in that reference. Glaxo Inc. v. Novopharm Ltd., 52 F.3d 1043, 1047-48 (Fed Cir. 1995). "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly

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present” in the anticipating reference. Trintec Indus., Inc. v. Top-USA Corp., 295 F.3d 1292, 1295 (Fed. Cir. 2002).

Anticipation also requires that the prior patent “be enabling, such that one of the ordinary skill in the art could practice the invention without undue experimentation.” Novo Nordisk Pharm., Inc. v. Bio-Tech Gen. Corp., 424 F.3d 1347, 1355 (Fed. Cir. 2005). “A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.” Elan Pharm., Inc. v. Mayo Found. for Med. Educ. Research, 346 F.3d 1051, 1054 (Fed Cir. 2003).

Finally, anticipation is a question of fact. SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1343 (2005).

2. Findings of Fact and Conclusions of Law

a. The Murakami Patent

Teva argues that Murakami discloses claims 3, 34, and 40 of the '344 Patent, claims 76, 106, 112, and 160 of the '953 Patent, claims 1, 2, 6, 8, 9, and 12 of the '362 Patent, and claims 2 and 6 of the '645 Patent, and, therefore, these claims are invalid for anticipation. According to Teva, Murakami teaches a formoterol composition with the same ingredients and proportions as the claimed compositions. (Dkt. No. 249). Further, Teva argues that

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Murakami teaches a person of ordinary skill in the art to formulate an inhalation solution of formoterol. Id. Dey disputes this, asserting that Murakami does not disclose the compositional and stability elements of the Asserted Claims, nor does it enable a person of ordinary skill in the art to formulate an inhalation solution of formoterol. (Dkt. No. 250).

After careful consideration of these arguments, the Court concludes that the Murakami Patent does not anticipate the Asserted Claims. In November, 1976, more than a year before the '344, '953, and '645 Patents were filed, Murakami (TX 16) was issued to Yomanouchi Pharmaceutical Co. Ltd., and therefore is prior art for purposes of § 102(b). The PTO considered the Murakami Patent during the prosecution of the '344, '953, and '654 Patents, and allowed them over Murakami. (Tr. 947:20-23 (Hendelees).) Although the PTO's decision with respect to anticipation is not binding on this Court, it is material evidence that the Court "must consider in determining whether the party asserting invalidity has met its statutory burden by clear and convincing evidence." Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1555 (Fed. Cir. 1985).

Murakami claims a set of compounds, including the formoterol molecule, from a family of molecules that it describes as effective bronchodilating agents. (TX 16, 1:54-57, 38:33-66; Tr. 233:21-

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234:6 (Barnes).) The claimed set comprises a large number of compounds and contains examples of how to synthesize specific compounds, including formoterol. (TX 16, 17:13-37:52; Tr. 238:5-7 (Barnes), 585:7-586:7; 587:3-588:4 (Myrdal).)

Murakami states that the compounds it describes may be administered in various ways, including "orally," "subcutaneously, intramuscularly, or intravenously as injections" or "in the form of aerosols as inhalations." (TX 16, 7:65-8:3). Importantly, however, the patent only discloses three pharmaceutical formulations of the claimed compounds. Those formulations are designated as either "injectable," "for injection," or tablets. (Tr. 234:11-10, 237:24-238:12 (Barnes).)

Although the parties agree that Murakami is prior art to the '344, '953, and '654 Patents, they disagree as to whether it discloses all of the limitations of the Asserted Claims, and whether it enables a person of ordinary skill in the art to formulate an inhalation solution of formoterol. The Court therefore turns next to this issue.

**1) The Murakami Patent's Disclosures of the
Compositional Elements of the Asserted Claims**

Murakami discloses injectable solutions containing a hydroxyl analogue, a molecule structurally similar to formoterol. It does

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not, however, disclose an aqueous formulation that either contains formoterol or is suitable for inhalation by nebulization, both of which are components of every Asserted Claim. (Tr. 780:6-16 (Hendeles).)

Teva characterizes Murakami as teaching "aqueous formoterol formulations," even though its own experts admitted that the Murakami formulations do not contain formoterol. (Tr. 588:5-9, 589:8-14 (Myrdal), 982:19-21 (Hendeles).) Teva attempts to classify the hydroxyl analogue contained in Murakami as a derivative of formoterol. Notably, however, while the hydroxyl analogue is structurally similar to formoterol, it was not prepared, synthesized, or derived from formoterol. (TX 16, 11:12-12:41, 19:47-68).

Teva dismisses this critical defect, arguing that, because Murakami describes a molecule similar to formoterol, a formulator could have chosen to swap formoterol with the molecule that was used, and the new formulation then would have anticipated the Asserted Claims. As Dey pointedly notes, however, the law does not allow for a mix and match approach to anticipation. Rather, the identical invention must be described in the prior art reference in order for an anticipation defense to be successful. See Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1083-84 (Fed. Cir. 2008)

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("The anticipating reference must clearly and unequivocally disclose the claimed invention or direct those skilled in the art to the invention without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference."). Thus, Teva has failed to establish, by clear and convincing evidence, that the compositional elements of the Asserted Claims are inherently disclosed by Murakami. Glaxo, 52 F.3d at 1043.

2) The Murakami Patent's Disclosures of the Stability Elements of the Asserted Claims

Unlike a majority of the Asserted Claims, Murakami does not disclose any specific stability limitations.⁵ To overcome this gap, Teva relies on the opinion of Dr. Myrdal that the experiments performed by Dr. Robert O. Williams in 2009, which examined the long-term stability of a formulation similar to Murakami, establish that Murakami inherently discloses a stability limitation. Unfortunately for Teva, Dr. Myrdal acknowledged during his testimony that the composition tested by Dr. Williams cannot be found anywhere in the Murakami Patent. (Tr. 593:18-19).

⁵ Only eight of the twenty-eight Asserted Claims do not recite a specific stability limitation: claims 4, 6, 8, 12, and 15 of the '362 Patent and claims 6, 8, and 9 of the '645 Patent.

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Furthermore, unlike Murakami's formulation, Dr. Williams's formulation was oxygen free, a fact that could have significantly influenced the formulation's stability. (Tr. 696:2-7 (Myrdal).) Hence, Dr. Myrdal's opinions of Murakami's stability, based as they are on Dr. Williams's experiments, are merely speculative and inadequate to establish, by clear and convincing evidence, that a stability limitation is inherently disclosed by Murakami. Glaxo, 52 F.3d at 1043.

3) Enablement

In order to anticipate the Asserted Claims, Murakami must also enable a person of ordinary skill in the art to practice the invention without undue experimentation. Novo Nordisk Pharm., 424 F.3d at 1347. "Whether a prior art reference is enabling is a matter of law based upon underlying factual findings." Id.

When a prior art patent is asserted as evidence of an invalidity defense, as is the case here, the Court must presume that the prior art patent is enabling, and the patentee has the burden of overcoming that presumption. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1355 (Fed Cir. 2003). If the patentee satisfies that burden by setting forth "evidence of nonenablement that a trial court finds persuasive, the trial court

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must then exclude that prior art patent in any anticipation inquiry.” Id.

Dey argues that the Murakami Patent does not enable a person of ordinary skill in the art to practice the Asserted Claims without undue experimentation because nothing in the patent indicates that an injectable formulation could be derived from its components. Teva asserts in response that Murakami teaches an inhalable solution by explaining that the compounds it discloses can be delivered as aerosols.

As Dr. Barnes testified, however, this explanation was part of a disclosure listing “every conceivable way of giving a drug to a human,” and could not possibly be sufficient to teach one of ordinary skill how to make a solution of formoterol by nebulization without undue experimentation. (Tr. 235:24-236:3 (Barnes).). Thus, it is not clear that a person of ordinary skill in the art would understand from Murakami how to create a solution suitable for nebulization.

Further, an anticipating reference must also enable a person of ordinary skill in the art to practice the *invention* without undue experimentation. Impax Labs., Inc. v. Aventis Pharm. Inc., 545 F.3d 1312, 1314-16 (Fed. Cir. 2008). Thus, even if Teva were able to prove that Murakami’s disclosure of an injectable solution

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enables nebulizer solutions, it must also teach a person of ordinary skill in the art to formulate a solution that 1) contains formoterol, and 2) achieves long-term stability. Nothing in the Murakami Patent indicates that a person of ordinary skill in the art would be able to make these deductions, considering the patent discloses different compositional and stability elements from the Asserted Claims.

4) Conclusion

The Murakami Patent does not disclose, either expressly or inherently, every required limitation of claims 3, 34, and 40 of the '344 Patent; claims 76, 106, 112, and 160 of the '953 Patent; claims 1, 2, 6, 8, 9, and 12 of the '362 Patent; and claims 2 and 6 of the '645 Patent. Nor does it enable a person of ordinary skill in the art to formulate an inhalation solution of formoterol. Thus, the Murakami Patent does not "disclose each and every limitation" of the Asserted Claims, and therefore does not anticipate and invalidate these claims. Schering, 339 F.3d 1377.

b. The Gao Patent

Teva next argues that, because the Gao Patent discloses all of the elements of claims 3 and 34 of the '344 Patent, and claims 75 and 106 of the '953 Patent, these claims are invalid for

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anticipation. (Dkt. No. 249). It asserts that, consistent with the Asserted Claims, Gao contains a formoterol concentration suitable for broncholization by nebulization without prior dilution. Further, Teva argues that the formulation described in Gao has the same inherent stability, shelf life, degradation rate, and short term storage ability as the claimed composition. Id. Dey contends that the Gao Patent differs from the Asserted Claims in critical ways-namely, in its compositional and stability elements-thus preventing anticipation. (Dkt. No. 250). Dey has the better argument.

The Gao Patent was issued to Sepracor in March of 2000. Since it issued more than a year before the First Family patents were filed on April 17, 2001, it is prior art for purposes of § 102(b). The PTO considered the Gao Patent during the prosecution of the First Family patents, and allowed these patents over it. (Tr. 947:20-23 (Hendeles).)

The Gao Patent describes a salt form of the optically pure formoterol compound called "arformoterol," along with the compositions containing it. (TX 15, 20:33-59). The patent also specifies methods of preparing the compound. (TX 14, 1:11-14). Gao's focus is stereochemical separation. It teaches "an approach to long-term storage of dosage forms for aqueous aerosols," which

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is described in a co-pending patent application known as the Redmon Patent. (TX 15, 20:6:10).

The Redmon Patent does not teach stable aqueous formulations, but instead describes a method for "preparing aerosols of water-sensitive medicaments" using a pharmaceutical kit consisting of a two-chambered device (TX 17 at DEY-TV0177979). One chamber, which is "substantially water-impermeable," holds a solid-state matrix form of the medicament and a carrier material, while the second container holds a "sufficient quantity of an aqueous vehicle to dissolve the matrix network within fifteen seconds." (TX 17, 2:13-20). According to Redmon, this two-chamber solution was necessary because, while "water is the only vehicle that can reasonably be employed in nebulization, the medicament is itself not sufficiently stable in an aqueous environment to provide a practical shelf life for the aqueous formulation." (TX 17, 1:52-55). The parties agree that the Gao Patent is prior art to the First Family Patents, but disagree as to whether it discloses all of the limitations of claims 3 and 34 of the '344 Patent and claims 75 and 106 of the '953 Patent.

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**1) The Gao Patent's Disclosures of the Compositional
Elements of the Asserted Claims**

i) Concentration

Gao's formulation has an arformoterol free base concentration of 139 μ mL. (Tr. 473:14-23 (Myrdal), 813:18-20 (Hendeles).). The formoterol concentration in the Gao formulation thus exceeds 50 μ mL, which is the highest formoterol concentration disclosed in any Asserted Claim specifying a concentration.

Despite Gao's high formoterol concentration, Teva asserts that, based on Dr. Barnes's testimony, the drug is still "effective for bronchodilation by nebulization" and "suitable for direct administration by nebulizer without dilution." (Dkt. No. 249). However, Dr. Barnes did not testify that 139 μ g/mL is suitable for direct administration by nebulizer without dilution; rather, he noted that 200 μ g/mL was described in, but not within the scope of, the '344 Patent. (Tr. 320:6-22). Further, he specifically stated that a 139 μ g/mL concentration would be "too high" for the long term treatment of COPD. (Tr. 315:24-316:2, 320:2-5 (Barnes).)

Dr. Barnes's testimony that a 139 μ g/mL formoterol concentration is too high for the long-term treatment of COPD is consistent with the distinction drawn by Dey during the reexamination of the First Family patents. At the reexamination,

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Dey overcame an anticipation objection based on Gao by arguing that the formulation in Dey's claims did not encompass concentrations of 139 µg/mL and up. (TX 3 at Dey-TV1730555 (n.14).) Thus, as a matter of law, this distinction defines "suitable for direct administration" for these patents as being limited to concentrations below 139 µg/mL. See SanDisk Corp. v. Memorex Prods., Inc., 415 F.3d 1278, 1286 (Fed. Cir. 2005) ("When the patentee makes clear and unmistakable prosecution arguments limiting the meaning of a claim term in order to overcome a rejection, the courts limit the relevant claim term to exclude the disclaimed matter.").

ii) Buffer Concentration, Ionic Strength, and Salinity

Gao fails to disclose any specific buffer concentration, ionic strength, or salinity. (Tr. 699:13-25, 700:17-22 (Myrdal), 977:17-19 (Hendeles), 1418:3-10 (Hastedt).) Thus, it does not anticipate any claim reciting a specific buffer concentration, including claim 74 of the '344 Patent and claim 136 of the '953 Patent, which both recite a buffer concentration of "about 20mM," or any of the Asserted Claims of the '362 or '645 Patents, which provide a buffer concentration range. Further, it does not anticipate claim 34 of the '344 Patent and claim 106 of the '953 Patent, which recite

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iconic strengths of .05 to .16, or claim 116 of the '344 Patent, and claim 163 of the '953 Patent, which require isotonic saline solution.

iii) Dosage

The formulation disclosed in Gao is not suitable for a single unit dosage. (Tr. 977:9-16 (Hendeles).) Thus, Gao does not anticipate claims 104 and 116 of the '344 Patent, claims 160 and 163 of the '953 Patent, and each of the Asserted Claims of the '362 and '645 Patents, all of which require a single unit dose.

2) The Gao Patent's Disclosures of the Stability Elements of the Asserted Claims

Unlike a majority of the Asserted Claims;⁶ Gao does not disclose any specific stability limitations. Rather, it describes a formulation that has "problematic stability" and is "not attractive for long term storage." (TX 15, 20:1-6).

Teva attempts to overcome this defect by arguing that the Gao formulation "inherently" meets the stability requirements of the Asserted Claims. (Dkt. No. 249). Its argument relies on the opinion expressed by Dr. Hendeles that, based on his examination of Dr. Williams's experimental report, Gao inherently met the stability

⁶See *Supra* Note 6.

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requirements of the Asserted Claims. (Tr. 856:11-15, 1009:9-1010:7 (Hendeles).).

Dr. Hendeles, however, failed to note that the formulation tested by Dr. Williams was his own invention, not Gao's. Although Dr. Williams created a drug with a citrate buffer concentration of 5 and 50mM, Gao does not teach any specific buffer concentration. Thus, it is likely that Gao's formulation and the formulation of Dr. Williams have different stabilities. (Tr. 699:13-17, 700:1-5, 700:17-22 (Myrdal), 1431:22-1433:22 (Hastedt).) Dr. Williams's test results therefore cannot definitively predict Gao's actual stability. Accordingly, Gao does not anticipate any of the Asserted Claims that contain stability limitations.

3) Conclusion

Because the Gao Patent does not "disclose every limitation" of claims 3 and 34 of the '344 Patent, or claims 76 and 106 of the '953 Patent, it does not anticipate and therefore invalidate these claims. Schering, 339 F.3d at 1377.

c. Sepracor Transaction

Teva contends that the Asserted Claims are invalidated by the on-sale bar of 35 U.S.C. § 102 (b), due to Sepracor's transactions with ALP. (Dkt. No. 249). Dey, however, argues that Teva has

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failed to establish, by clear and convincing evidence, that the elements of the on-sale bar have been met in this case. (Dkt. No. 254). Dey's arguments are the most persuasive.

1) Factual Background

From the late 1990s until the early 2000s, the pharmaceutical company, Sepracor, developed Brovana[®], a drug containing arformoterol in an aqueous solution.⁷ (Tr. 1328:15-19 (Wald).) In the course of developing Brovana[®], Sepracor discovered a way to manufacture arformoterol, the stereochemically pure active ingredient in formoterol. (Tr. 1340:7-23 (Wald).)

⁷ Apart from this action, Dey has successfully prosecuted claims of infringement of the patents-in-suit against Sepracor based on its marketing of Brovana[®]. Dey, Inc. v. Sepracor, Inc., 847 F.Supp.2d 541, 547 (S.D.N.Y. 2012). On March 1, 2012, the United States District Court for the Southern District of New York granted Sepracor's motion for partial summary judgment, finding that the patents-in-suit were invalid under the on-sale bar of 35 U.S.C. § 102(b) based on Sepracor's use of Dey's invention in clinical trials more than one year before Dey's filing of the second family patents. Id.

In May of 2013, the Federal Circuit held that Brovana[®] infringed Dey's valid Perforomist[®] patents. Dey, Inc. v. Sepracor, Inc., 715 Fed. Cir. 1351 (Fed. Cir. 2013). Following the Federal Circuit's decision, Sepracor stipulated to the infringement and validity of Dey's patents, and the district court entered a final judgment reflecting this. (TX. 864). Sepracor continues to market Brovana[®] pursuant to a licensing agreement with Dey, and Teva does not dispute that Brovana[®] infringes the patents-in-suit. (Tr. 516:11-12).

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Sepracor outsourced the preparation of several test batches of a packaged aqueous solution containing the arformoterol it owned and manufactured to a "contract packager," ALP. Sepracor contracted with ALP to utilize their packaging service because Sepracor did not own the necessary "blow-fill-seal" packaging equipment. Throughout their various transactions, Sepracor provided ALP with the arformoterol it had manufactured, together with precise specifications for the formulation ALP was to mix and package. ALP then prepared the product according to Sepracor's specifications. Sepracor paid ALP for providing its services, labor, and expertise in mixing and packaging the formulations. (Tr. 1342:17-25, 1345:2-5 (Wald).)

In total, ALP prepared the following three formulations for Sepracor:

- 1) Lot No. 02797A: 100 µg/mL arformoterol concentration, packaged with 15 mL citrate buffered saline solution in 20 mL bottle. Manufactured in November of 1997;
- 2) Lot No. 01799B: 96 µg/mL arformoterol concentration, packaged in 7 mL citrate buffered saline solution in 20 mL bottle. Manufactured in July of 1999; and

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3) Lot No. 03501A: 15 µg/2 mL arformoterol concentration, packaged in 2 mL citrate buffered saline solution in 2 mL vials. Manufactured in July of 2001.

(TX 509). Sepracor used the Lots packaged by ALP exclusively in its clinical trials of Brovana®. (Tr. 1342:17-25, 1345:2-5 (Wald).)

2) Standard of Law

Patent law denies a patent to an inventor who applies for a patent more than one year after making an attempt to profit from his invention by putting it on sale. 35 U.S.C. § 102(b); Atlanta Attachment Co. v. Leggett & Platt, Inc., 516 F.3d 1361, 1365 (Fed. Cir. 2008). An invention is so barred from patenting when it was both the subject of a commercial offer or sale before the critical date and also ready for patenting at the time of offer. Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 67, 199 S.Ct. 304, 311-12 (1998). Furthermore, "the court should determine whether the subject of the barring activity met each of the limitations of the claim, and thus was an embodiment of the claimed invention." Atlanta Attachment Co., 516 F.3d at 1365.

The overriding concern of the on-sale bar is that an inventor may attempt to commercialize his invention beyond the statutory term. Netscape Commc'ns. Corp. v. Konrad, 295 F.3d 1315, 1323 (Fed. Cir. 2002). The on-sale bar, thus, seeks to prevent an inventor

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from extending his monopoly by the expedient of first commercially selling his offer for a time and then later applying for a patent.

An inventor who seeks to perfect his discovery through experimentation, however, may conduct extensive testing without losing his right to a patent, even if such testing occurs in the public eye. Netscape, 295 F.3d at 1323. The law has long recognized a distinction between experimental usage and commercial exploitation of an invention. "While any attempt to use [an invention] for profit...would deprive the inventor of his right to a patent," and inventor's use "by way of experiment," does not bar patentability. Atlanta Attachment Co., 516 F.3d at 1365. Thus, the Court must consider "whether the suspect activities were experiments as opposed to an attempt to profit from the invention, that is, whether the primary purpose of the offers and sales was to conduct experimentation." Allen Eng'g Corp. v. Bartell Indus., 299 F.3d 1336, 1354 (Fed. Cir. 2002).

3) Analysis

i) Commercial Offer for Sale

As noted, the on-sale bar only applies if an invention was subject to a prior "commercial offer for sale." To meet this requirement, the offer must be sufficiently definite such that

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another party could make a binding contract by simple acceptance, assuming consideration. Netscape, 295 F.3d at 1323. In determining such definiteness, the Court must review the language of the proposal in accordance with the principles of general contract law. Id.

Contract law distinguishes between sales for commercial versus experimental purposes. Id. While “[a]ny attempt to use [an invention] for profit ... would deprive the inventor of his right to a patent,” an inventor's use “by way of experiment” does not bar patentability. Elizabeth v. Am. Nicholson Pavement Co., 97 U.S. 126, 137 (1877). Thus, the Court must determine whether the “sale” of the Sepracor Lots to ALP was done for experimental, rather than commercial, purposes.

Dey contends that the transactions between Sepracor and ALP were purely experimental. (Dkt. No. 250). Teva responds that Dey has failed to establish that the on-sale bar is not applicable in this instance. (Dkt. No. 253).

As described by Dey, the arrangement between Sepracor and ALP was a “contract for services,” not the sale of a product. (Tr. 1345:5 (Wald).) Pursuant to Sepracor’s contract with ALP, Sepracor would provide, among other things, active and excipient raw materials, along with “complete product and packaging

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specifications," while ALP would provide, among other things, "blow/fill/seal machinery and associated support equipment," "in-process testing," and "finished product testing," it being "understood that [ALP] is a packager pursuant to [Sepracor's] specifications." (TX 436; TX 449.1; TX 488.1). Further, ALP made "no warranties, express or implied, as to the efficacy of the packaged product." *Id.* The Lots were then used exclusively by Sepracor for its clinical trials. (Tr. 1353:5-9 (Wald).) This evidence establishes that the primary purpose of Sepracor's transaction with ALP was experimental, not commercial.

Teva contends that there is no "supplier exception" to the on-sale bar. (Dkt. No. 249). Teva's argument misapprehends the issue. Dey never attempted to argue that the on-sale bar is inapplicable because ALP was merely a "supplier" to Sepracor. In the contrary, consistent with the case law, Dey's argument has always been that there was no "sale," because ALP merely served as a contract "packager," and the packaged Lots were only used for experimental purposes. (TX 436; TX 449:1, TX 448.1). Consistent with Dey's arguments, the evidence adduced at trial failed to establish that the transaction between Sepracor and ALP constituted a "commercial sale."

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ii) Sale of the Invention

The on-sale bar requires that there be a sale of the entire claimed invention. 35 U.S.C. § 102(b). Here, even if the contract between ALP and Sepracor could be construed as a “commercial sale,” the contract did not embody all the elements of the “invention” claimed in Dey’s patents. It is undisputed that, at no time, did Sepracor surrender ownership to ALP of the active ingredient, formoterol, which is an element of every Asserted Claim. As a result, ALP never sold the complete “invention” to Sepracor. Sepracor owned the core component—formoterol—of the solutions ALP packaged at Sepracor’s request.

The Federal Circuit allows inventors, such as Sepracor, to “request another entity’s services in developing products embodying the invention without triggering the on-sale bar.” Trading Techs. Int’l, Inc. v. eSpeed, Inc., 595 F.3d 1340, 1361-62 (Fed. Cir. 2010). To hold otherwise would disadvantage small pharmaceutical companies who “fairly common[ly]” outsource mixing and packaging “because of [the] capital investment and specialized knowledge required to operate the machinery.” (Tr. 1332:20-23 (Wald).) Therefore, Teva has failed to establish, by clear and convincing evidence, that there was a “commercial sale” of Dey’s “invention.”

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iii) Public Nature of the Sale

The on-sale bar also requires that the sale of an invention be public. The bar is not triggered when a third party, unaffiliated with the inventor, sells a non-public invention in a manner that does not give the public access to the transaction. W.L. Gore & Assos., Inc. v. Garlok, Inc., 721 F.2d 1540, 1550 (Fed. Cir. 1983). This is because such sales neither create an expectation that an unpatented invention is in the public domain nor constitute pre-application commercial exploitation of an invention by the inventor-the policies that the on-sale bar attempts to further. Id.

Here, it is uncontested that Dey was not a party to the transaction between ALP and Sepracor. Thus, the on-sale bar is not triggered by the parties' private transaction. Id.

iv) Timing of the Transaction

The on-sale bar only applies to inventions sold one year prior to the application for a patent. Atlanta Attachment Co. v. Leggett & Platt, Inc., 516 F.3d 1361, 1365 (Fed. Cir. 2008). The parties do not dispute that the 3501 Lot was packaged by ALP in July, 2001. (TX 509). It is also undisputed that the provisional application for the First Family patents was not filed until April 17, 2001. Thus, ALP packaged and transferred the 3501 Lots only after the

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provisional application was filed for the First Family patents; therefore, the transfer of the 3501 Lots cannot invalidate those patents.

v) Composition of the Sepracor Lots

The on-sale bar invalidates a patent under § 102(b) only if the subject of the barring activity practiced every limitation of the Asserted Claims. ResQNet.com v. Lansa, Inc., 594 F.3d 860, 866-67 (Fed. Cir. 2010). Dey contends that two of the three Sepracor Lots, Lots 2797A and 1799B, fail to practice one or more limitations of the Asserted Claims. In its response, Teva asserts that Dey has misconstrued the true composition of the Sepracor Lots.

(a) . Unit Dosage

Lots 2797A and 1799B were packaged and transferred to Sepracor in large volumes (15 mL and 7 mL quantities, respectively). Accordingly, the Lots were not packaged as “unit doses,” or in a “quantity that is [to be] taken or administered at one time,” as is required by several of the Asserted Claims.⁸ (Tr. 1378:21-1379:8 (Wald), 977:9-16 (Hendeles).)

⁸The following claims require unit doses: claims 65, 104, and 116 of the '344 Patent; claims 160 and 163 of the '953 Patent; and each Asserted Claim of the '342 and '645 Patents.

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Teva attempts to overcome this gap by claiming that the Lots were eventually apportioned into unit doses when they were used in clinical trials. (Dkt. No. 249). However, the fact that the Lots had the potential to be apportioned into unit doses after they were “sold” is irrelevant to a determination of whether the Lots “as sold” anticipated the Asserted Claims. A court must analyze the composition of the potentially anticipating formulation at the time of its sale. Schaltech Inc. v. Retec/Tetra, L.L.C., 178 F.3d 1378, 1383 (Fed. Cir. 1999). Here, Lots 2797A and 1799B were not packaged as unit doses at the time of sale, and thus, do not anticipate the Asserted Claims that require packaging as unit doses.

(b). Stability

Unlike the Asserted Claims, Lots 2797A and 1799B did not disclose stability limitations. Although Dr. Myrdal made certain projections of stability based on Sepracor data concerning the shelf life of the Sepracor Lots, he failed to conduct any analysis of how much formoterol would remain in the formulation after one year. Thus, his findings fail to establish whether the Lots exhibit long-term stability. (Tr. 704:1-706:21 (Myrdal).)

To overcome this defect, Teva contends that, because the Lots have “all of the components of the composition of the Asserted

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Claims," they must have the same "inherent stability." (Dkt. No. 249). However, as discussed earlier, because the compositions of the Lots are not identical to the Asserted Claims, positing that they exhibit the same "inherent stability" is speculative. Lots 2797A and 1799B therefore do not anticipate the Asserted Claims that disclose stability elements.

(c). Concentration

It is uncontested that the concentration of 2797A and 1799B was 100 µg/mL and 96 µg/mL, respectively. These Lots, therefore, are too highly concentrated to fall within any of the specific concentration ranges recited by several of the Asserted Claims, none of which exceeds 50 µg/mL. (Tr. 708 2-10 (Myrdal)). Thus, these Lots cannot anticipate claims 40, 104, and 116 of the '344 Patent, claims 112, 160, and 163 of the '953 Patent, and each Asserted Claim of the '362 and '645 Patents.

4) Conclusion

The Sepracor Lots were not subject to a commercial sale in the one year prior to the time Dey applied for its patents. Further, the Lots differ in composition from the Asserted Claims. Consequently, the Asserted Claims are not invalidated by the on-sale bar of 35 U.S.C. § 102(b).

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d. Conclusion as to the Defense of Anticipation

Because there is no clear and convincing evidence that the prior art discloses each and every limitation of the claimed invention, the Asserted Claims are not invalid for anticipation.

B. Obviousness

1. Standard of Law

A patent will be invalid pursuant to 35 U.S.C. § 103 when “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc., 701 F.3d 698, 706-07 (Fed Cir. 2013). “Generally, a party seeking to invalidate a patent as obvious must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had the reasonable expectation of success in doing so.” Id. “The Supreme Court has warned, however, that while an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness

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inquiry must be expansive and flexible.” Id. at 707 (citing KSR Int’l Co. v. Teleflex Inc., 550 U.S. 398, 415, 127 S.Ct. 1727, 167 L.E.2d 705 (2007)). The concern with granting patents in spite of obviousness is that doing so would allow parties to obtain a monopoly over inventions already known in a given field, discouraging innovation. KSR Int’l Co., 550 U.S. at 416.

A claim must have been nonobvious “at the time the invention was made.” 35 U.S. § 103(a). A court therefore must avoid the use of hindsight in this analysis and go beyond “simply retracing the path of the inventor.” Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008).

In Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18, 86 S. Ct. 684, 694-95 (1966), the Supreme Court of the United States established the following four-part test for determining obviousness:

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is to be determined. Such secondary considerations as commercial success, long felt but unresolved needs, failures of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

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Any analysis of obviousness therefore must include a consideration of secondary, objective indicia. Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc., 711 F.3d 1348, 1368 (Fed. Cir. 2013). These considerations include "copying, long felt but unresolved need, failure of others, commercial success, unexpected results created by the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans before the invention." Id.

"The ultimate judgment of obviousness is a legal determination." KSR Int'l Co., 550 U.S. at 417. However, the obviousness inquiry also involves factual determinations within the framework of the Graham factors. Sakaraida v. Ag. Pro, Inc., 425 U.S. 273, 280, 96 S.Ct. 1532 (1976).

2. Findings of Fact and Conclusions of Law

The Court begins its obviousness analysis with a discussion of the Graham factors. 383 U.S. at 17-18.

a. Scope and Content of the Prior Art

It is undisputed that the Murakami and Gao Patents, as well as the Puigbó (TX 635) and Gavin (TX 95) articles, are part of the relevant prior art for the patents-in-suit. As discussed earlier, the parties agree that Murakami and Gao are prior art to

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the Asserted Claims. Murakami discloses a set of bronchodilating agents. (TX 16, 1:54-57, 38:33-66; Tr. 233:21-234:6 (Barnes).) The claimed set comprises a large number of compounds and contains examples of how to synthesize specific compounds, including formoterol. (TX 16, 17:13-37:52; Tr. 238:5-7 (Barnes), 585:7-586:7; 587:3-588:4 (Myrdal).) Further, Murakami Example 34 discloses an injectable formulation containing a hydroxyl analogue, a molecule structurally similar to formoterol.

Gao discloses an aqueous formulation of formoterol. It relates to optically pure isomers of formoterol and teaches an aqueous aerosol formulation for nebulization that is "quite suitable for short term use" but "not attractive for long term storage" at room temperature. (TX 15).

The parties further agree that the Puigbó and Gavin articles are prior art to the Asserted Claims. Both articles discuss experiments related to the treatment of respiratory diseases and were considered by the PTO during the prosecution of the patents-in-suit. (Tr. 947-20-23 (Hendeles).)

The Puigbó article was published in 2000 and is prior art to the Second Family patents. It describes experiments by Dr. A. Perez Puigbó to treat asthma exacerbations by administering unit doses of formoterol fumarate by nebulization. (TX 625). Puigbó

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discloses dissolving a single dose of dry Foradil® formoterol fumarate powder in 2 mL of 0.9% sterile saline solution. Id. The pH of the Puigbó composition was 5.5 and the concentration was approximately 6 µg/mL. Id.

The Gavin article was published in October, 2001 and is prior art to the Second Family patents. (TX 95). It describes compositions for treating respiratory diseases. In pertinent part, Gavin discloses formoterol (in combination with fluticasone) in an aqueous nebulizer formulation that includes polysorbate 20 and sorbitan monolaurate. Id.

The parties disagree as to whether the Sepracor Lots are part of the prior art. Teva argues that they are prior art because their compositions are virtually the same in scope as the compositions in Dey's patents. (Dkt. No. 249). Dey contends that the Sepracor Lots cannot be prior art because they were not sold or publicly disclosed. (Dkt. No. 254).

As the Court has already concluded, the Sepracor Lots were not "on-sale" within the meaning of § 102(b), and, thus, are not considered prior art under either § 102 or § 103. Further, even if the Lots had been "on sale," and therefore considered prior art under § 102, their non-public status would still prevent them from being relevant under § 103. In re Newell, 891 F.2d 899, 901 (Fed.

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Cir. 1989). Obviousness is concerned with public knowledge-what a person of ordinary skill in the art would actually know based on the prior art. *Id.* Such a person would not be aware of non-public materials, such as the Lots that ALP confidentially delivered to Sepracor.

b. Differences Between the Prior Art and the Claims at Issue

Unlike the Asserted Claims, Murakami does not disclose an aqueous formulation that either contains formoterol or is suitable for inhalation by nebulization, nor does it contain any stability limitations. While Gao does teach an aqueous solution of formoterol, it does not disclose a formulation with long-term stability, but rather describes a formulation with problematic stability. It also fails to disclose any specific buffer concentration, ionic strength, or salinity, and it also describes a formulation not suitable for single unit dosage.

Furthermore, unlike the Asserted Claims, it is undisputed that the Gavin article fails to disclose the pH or the stability of the experimental formulation. (Tr. 252:16-18 (Barnes).) Similarly, the Puigbó article does not discuss stability. (Tr. 248:21-250:7 (Barnes).) That Puigbó does describe a process of administering the formoterol solution immediately after preparation only aids the

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conclusion that the authors believed the solution would not exhibit long-term stability. (TX 625).

c. Level of Skill in the Art

The parties agree that a person of ordinary skill in the art for purposes of this action would have either an advanced degree in pharmacy or a graduate degree in pharmaceuticals, along with several years of experience with pharmaceutical formulations, including basic formulation principles, pharmacology, and/or the treatment of pulmonary diseases. (Tr. 439:19-440:3, 751:15-25.)

The Federal Circuit has established a "teaching, suggestion, or motivation" test ("TSM test") to determine whether, in light of the prior art, an invention would have been obvious to a person of ordinary skill in the art. The TSM test provides that a claim will be rendered obvious only if there is "some motivation or suggestion to combine the prior art teachings" in either the prior art, the nature of the problem, or the knowledge of a person of ordinary skill in the art. Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1323-24 (Fed. Cir. 1999). The fact that all of the elements of a claimed invention were part of the prior art does not automatically render an invention obvious, since many inventions build on knowledge that is already known. KSR Int'l Co., 127 S.Ct. at 1727. Thus, there must have been some inherent motivation to combine the

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elements as done in the claimed invention in order for that invention to be invalid for obviousness. Id.

In KSR, the Supreme Court explained that the TSM test should not be reduced to a rigid formula. 127 S.Ct. At 1741. An "obvious analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." Id. A court may also consider "interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." Id. at 1740-41.

Thus, there need not be an explicit statement in the prior art itself suggesting the invention in order for the prior art to render the invention obvious. Rather, an issue in the relevant field present at the time of the creation of the invention can serve as a motivation to combine prior art elements. Id. at 1742. Furthermore, when an invention involves a combination of elements already known in the prior art, that invention is obvious unless

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"the improvement is more than the predictable use of prior art elements according to their established functions. Id. at 1741.

Likewise, if a combination would have been obvious to try at the time of the invention, that invention could be rendered obvious by the prior art. Id. However, if the prior art teaches against combining the known elements, then an invention that successfully combines those elements is likely nonobvious. United States v. Adams, 383 U.S. 39, 50-51, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966).

1) Combining the Prior Art References

Teva contends that, while no single prior art reference may have rendered Dey's invention obvious, a combination of those various references did. (Dkt. No. 249). Specifically, it argues that, through combining the following prior art disclosures, Dey's invention is rendered obvious:

- Gao discloses concentrations of formoterol "effective for bronchodilation" and formulations that could be used in a nebulizer;
- Murakami discloses "formoterol";
- Murakami discloses "sterile" solutions;
- Murakami, in Example 34, used a citrate buffer to generate a pH of 4 to 6 and Gao uses a citrate buffer to achieve a pH of 5; and

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- Other drugs have been “formulated for single dose administration.”

Id.

The fact that certain features are disclosed in the prior art, however, is insufficient to establish that a claimed invention is obvious. Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1549 (Fed. Cir. 1983). It is common to find elements of a claimed invention in the prior art. The test is “whether the claimed invention as a whole, in light of all the teachings of the references in their entirety, would have been obvious to one of ordinary skill at the time the invention was made.” Id.

Here, there is no evidence that any combination of the prior art would indicate that an aqueous formulation of formoterol with long-term stability was possible. From formoterol’s discovery in the 1970s until Dey’s development of Perforomist®, the primary method of maintaining formoterol’s stability was “keeping the powder dry.” (TX 15, 20:3-6). Gao restates the conventional wisdom—that formoterol’s stability in aqueous solution is “problematic” and “not attractive for long term storage.” Id.

Gao and Redmon suggested a two-chamber storage system that keeps the solid drug dry and separate from the aqueous solution until immediately prior to use in order to effectively store

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formoterol. (TX 15, 20:6-10; TX 17, 1:62-664, 2:12-62). Similarly, Puigbó suggests dissolving a dry powder formulation of formoterol in saline solution and administering it via nebulization immediately after the solution is prepared. (TX 625 at 74; Tr. 249:4-22 (Barnes), 624:8-11, 626:2-6 (Myrdal), 999:20-1000:2 (Henedeles).)

Thus, a person of ordinary skill reading the prior art in combination would understand that, to administer formoterol via nebulization, a user should keep the powder dry until just before use. That person would not understand that an aqueous formoterol solution could exhibit long-term stability. (Tr. 978:15-2, 1000:3-6 (Henedeles).) Therefore, there was no explicit motivation to combine the teachings set forth in the prior art, because those teachings taught against the elements Dey used to create its invention. KSR, 127 S.Ct. at 1738-39.

Furthermore, even if the elements of each Asserted Claim could be found somewhere in the prior art, any attack on the obviousness of Teva's invention would be entirely hindsight driven and therefore "legally incorrect." McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351 (Fed. Cir. 2001). A person of skill reviewing the prior art would not have had a reasonable expectation that a ready-to-use, stable formoterol formulation drawing upon those

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elements could be successfully made. The fact that the prior art taught compositional elements used to solve different problems that, in hindsight, turned out to be part of Dey's ultimate solution is not evidence that the solution was obvious. Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc., 725 F.3d 1341, 1352 (Fed. Cir. 2013). ("Obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fir the parameters of the patented invention."). Rather, only if, without the benefit of hindsight, "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so," Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed Cir. 2009), could a showing of obviousness be made. Teva has not established this by clear and convincing evidence.

2) Use of Standard Techniques

Relying on Dr. Myrdal's testimony, Teva also contends that the Asserted Claims are obvious because Dey's scientists used standard techniques in formulating their invention. (Dkt. No. 249). At trial, Dr. Myrdal opined that Dey did nothing more than apply "first principles" and "standard techniques" while doing "routine

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testing.” (Tr. 584:10-15.) He further testified that any invention arrived at in the same way would be considered obvious. Id.

Patent law, however, rejects the idea that novel inventions only arise from novel techniques. The process by which an invention was created is irrelevant to the analysis of its patentability. “Patentability shall not be negated by the manner in which the invention was made.” 35 U.S.C. § 103(a). Thus, contrary to Teva’s contentions, the use of routine techniques do not render an invention obvious. In re Yates, 663 F.2d 1054, 1056 n.4 (C.C.P.A. 1981) (“[T]he emphasis upon routine experimentation is contrary to the last sentence of section 103.”). Dey was therefore free to utilize standard, routine techniques in creating its invention without risking its patentability.

Furthermore, even though Dey’s scientists admitted to using routine techniques known in the scientific community, Dey did not seek out a patent based on the use of those routine techniques, but rather sought a patent based on formulations shaped by the results of those tests. As described above, those results were neither known nor predictable. (Tr. 90:18-21, 91:2-9, 125:2-127:18 (Chaudry).)

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3) Patenting Variations of the Prior Art

Finally, Teva argues that Dey's invention is obvious because its scientists merely patented minor variations of formulations Dey had discerned in the prior art based on their discovery of an "inherent" property (long-term stability) of those previously known formulations. (Tr. 1550:3-1555:6). Again, Teva relies on Dr. Myrdal's analysis of Dr. Williams's experiments, and his opinion that the "stability of the asserted claims would have been inherent property of the [prior art] compositions" such that these compositions "would have had the same stability and met the limitations of the [asserted] claims." (Tr. 434:3-11).

To the extent Teva is arguing that, based on Dr. Myrdal's analysis of Dr. Williams's testing, the formulations tested by Williams in 2009 inherently possessed the stability requirements of the Asserted Claims, this argument is irrelevant to a determination of whether those claims are obvious. Obviousness is concerned only with public knowledge, what a person of ordinary skill in the art would know based on the prior art. Newell, 891 F.2d at 901 ("A retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination."); 2-5 Chisum on Patents § 5.03[3][a][i][A] (2013 ed.) ("An inherent

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feature may be relied upon to establish obviousness only if the inherency would have been obvious to one of ordinary skill in the art: 'Inherency and obviousness are distinct concepts.'" (quoting Kloster Speedsteel AB v. Crucible Inc., 793 F.2d 1565, 1576 (Fed. Cir. 1986) (subsequently overruled on other grounds))). Thus, such data is not relevant to an assessment of whether the Asserted Claims were obvious; it was generated in 2009, and would not have been part of the knowledge of a person of ordinary skill in the art at the time Dey applied for its patents.

Moreover, as discussed above, the claimed formulations are too different from those in the prior art to argue effectively that the Asserted Claims possess the same "inherent" stability as those prior art formulations. To date, there is no reliable source of information about the stability of the actual Gao or Murakami formulations. (Tr. 186:12-14 (Chaudry).) Furthermore, Dey never attempted to test their stabilities. Instead, it undertook an independent and lengthy scientific process to identify the claimed formulations. Id. Thus, Teva has failed to establish that the Asserted Claims merely claim "inherent" properties obvious to a person of ordinary skill in the art.

In summary, there is no clear and convincing evidence that a person of ordinary skill in the art at the relevant time would have

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had the teaching, skill, or motivation to combine the prior art elements and create the claimed invention.

d. Secondary Considerations

Dey argues that secondary considerations of commercial success, satisfying a long felt need, and copying further illustrate the nonobviousness of the patents-in-suit. (Dkt. No. 250). Teva asserts that Dey failed to provide sufficient evidence to establish that objective indicia support a finding of nonobviousness. (Dkt. No. 253). Dey's arguments are more persuasive.

The Federal Circuit requires that, in addition to assessing the prior art, a court must examine evidence of "secondary considerations" of nonobviousness, if such evidence is available. Spectralytics, Inc. v. Cordis Corp., 649 F.3d 1336, 1344 (Fed. Cir. 2011). These considerations include "commercial success, long-felt but unresolved need, failure of others, and copying." Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 960 (Fed. Cir. 1986).

Such objective indicia "can be the most probative evidence of nonobviousness in the record, and enable the court to avert the trap of hindsight." Crocs, Inc. v. ITC, 598 F.3d 1294, 1310 (Fed. Cir. 2010). This is because the evidence "reflect[s] the

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contemporary view of the invention by competitors and the marketplace,” Spectralytics, 649 F.3d at 1344, and as such, is less susceptible to hindsight analysis.

The Court now examines each of the objective considerations raised by the parties.

1) Commercial Success

Initially, Dey contends that Perforomist® has been a commercial success due to its significant sales and profitability. (Dkt. No. 250). Teva asserts that, contrary to Dey’s contentions, Perforomist® has actually been a commercial failure with meager sales growth. (Dkt. No. 253).

Since its launch, Perforomist® has experienced stable sales growth. Between the years of 2007-2012, it generated \$278 million in profits, and Dey projects that net sales of Perforomist® will reach \$1 billion throughout the life of the product. (Tr. 1166:10-16 (Graybill).) Teva argues that these numbers illustrate that Perforomist® was a commercial disappointment, since the profits did not meet the company’s initial expectations.⁹ (Dkt. No. 249).

⁹ Dey initially invested 47.6 million dollars in the Perforomist® project, and originally projected that it would break even with costs and profits by early 2011, however, it took until late 2012 to do so. (Tr. 1068:4-1069:4).

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Commercial success is not automatically negated by the early issuance of overly optimistic internal projections. Allergan Inc. v. Apotex, Inc., No. 1:10-CV-681, 2013 U.S. Dist. LEXIS 13987 at *35-36 (M.D.N.C. Jan. 24, 2013). Looking at the numbers objectively, it is apparent that Perforomist® has been a commercial success. The product "is in the top deciles, the top quarter of well-performing drugs in the marketplace," and achieves a compound annual growth rate of 50%. (Tr. 1233:1-23, 1236:11-1237:5 (Rausser).)

Moreover, the fact that Teva has so vigorously attempted to launch a generic of Perforomist® may be considered a testament to its commercial success. As another court overseeing an ANDA case against Teva recently observed, "if the patented drug were not a commercial success, at least to some degree, generic manufacturers would have little interest in offering their own versions of the drug." Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 923 F.Supp.2d 602, 677 (D. Del. 2013). The same rationale applies here.

The commercial success of Perforomist® is a testament to the nonobviousness of the invention, since that success may be attributed to the specific features claimed in Dey's patents. "A *prima facie* case of nexus is made when the patentee shows both that

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there is commercial success, and that the product that is commercially successful is the invention disclosed and claimed in the patent.” Crocs, Inc. v. Int’l Trade Comm’n, 598 F.3d 1294, 1310-11 (Fed Cir. 2010).

Perforomist® has not been successful merely because it is manufactured by Dey or because of Dey’s marketing efforts. Rather, Perforomist® has achieved commercial success because it is an easy to use, non-DPI nebulizer formulation suitable for long term storage—the exact features for which Dey sought patent protection. This is illustrated by the fact that COPD patients have shown a preference for Perforomist® and are willing to pay a premium for the easy to use product. Medicare reimbursement, as Teva concedes, also favors Perforomist®.

Thus, Dey has made a clear showing of the commercial success of its product, which Teva has failed to successfully rebut. Performist’s® commercial success supports the conclusion that Dey’s invention was not obvious.

2) Long-Felt, Unresolved Need

Dey asserts that the creation of Perforomist® satisfied a long-felt, unresolved need for a non-DPI inhalation formulation of formoterol. (Dkt. No. 250). Teva argues that the needs of COPD

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patients were effectively served by the MDI and DPI products already in the marketplace. (Dkt. No. 253).

Prior to the launch of Perforomist®, there were no non-DPI inhalation formulations of formoterol available for commercial sale. Rather, when Dey applied for its patents, the only inhalable formoterol product approved for sale in the United States was Foradil®, a DPI formulation. (Tr. 228:8-24; 254:8-255:3; 256:1-8 (Barnes)). From this, Teva concludes that COPD patients were not in need of a product such as Perforomist. (Dkt. No. 24).

The need for a non-DPI inhalation formulation stemmed from the fact that many COPD patients lack the ability to effectively use DPIs, which require strength and cognitive skills to coordinate inhalation with manipulation of the devices. (Tr. 254:8-256:8 (Barnes), 47:22-48:10 (Chaundry)). In addition, DPIs require individuals to take a deep and forceful breath to deliver the drug to their lungs, which is the precise physical ability many COPD patients lack. (Tr. 222:15-223:7 (Barnes)). Nebulizers, however, avoid the inherent problems of DPIs, because they do not require coordination of actions while in use. Individuals need only breathe normally into the nebulizer in order to take their medication.

In 2001, the time when Dey applied for its first patent, the need for a non-DPI inhalation formulation was unmet. Several non-

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nebulizer formulations were considered, marketed, and often abandoned. These included oral products, such as those marketed by Yamanouchi; DPI products, such as Foradil®; and an MDI product that required refrigeration. Thus, no other company had satisfied the need for a non-DPI inhalation formulation until Dey introduced Perforomist® into the market. (Tr. 228:8-24 (Barnes)).

The existence of the need for an easy to use inhalation formulation is confirmed by the fact that physicians frequently prescribe Perforomist® to COPD patients. (Tr. 945:11-23 (Hendeles).) Additionally, insurance companies widely include Perforomist® on formularies, indicating that "the product is deemed valuable in having medical benefit to the patient." (Tr. 1168:3-1169:1) (stating that approximately 86% of insured lives have formulary plans including Perforomist®) (Graybill); (Tr. 1192:16-19) (Perforomist® appears on the most preferred tier for non-generic drugs in approximately 40% of formularies) (Graybill); (Tr. 954:6-958:7 (Hendeles)). Had there been no need for Perforomist®, it would be difficult to explain these statistics. In the Court's opinion, this history establishes that Dey's invention was not obvious prior to its inception.

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3) Copying

Dey argues that Teva's decision to copy the exact composition of Perforomist® illustrates that its invention was not obvious. (Dkt. No. 250). According to Teva, however, it was required to copy Perforomist® in order to obtain approval of its ANDA. (Dkt. No. 253).

Teva undisputably copied Dey's invention in its ANDA. "That . . . a large corporation with many engineers on its staff[] did not copy [the prior art], but found it necessary to copy the . . . claims in suit, is equally strong evidence of nonobviousness." Panduit Corp. v. Dennison Mfg. Co., 774 F.2d 1082, 1099 (Fed. Cir. 1985). Teva's assertion that the Hatch Waxman Act requires ANDA applicants to copy an already patented invention in order to be relieved from the Act's clinical safety requirements is unavailing.

Teva faced no requirement to copy Perforomist® in order to obtain approval of its ANDA. The Hatch Waxman Act only requires that an ANDA applicant copy certain attributes of an already approved product in order to be relieved from the Act's clinical safety trial requirements. Namely, the Act only requires that the applicant copy an approved drug's 1) active ingredient (e.g., Formoterol), 2) its route of administration (e.g., Oral

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Inhalation), and 3) its strength (e.g., 0.02 mg/2 ml). 21 U.S.C. 355j(2)(A)(ii)(I).

The Act does not require TEVA to copy Perforomist's® "inactive ingredients" or "excipients", which, here, are the features of Perforomist® that make aqueous formoterol suitable for long-term use. In fact, Teva's own experts agreed that "in showing bioequivalence [and thereby obtaining ANDA approval], you don't have to use the same excipients that the brand uses in formulating the generic product." (TX 1017, 38:13-16 (D'Abreu-Hayling)). Thus, Teva could have developed its own solution using different excipients, but instead chose to reverse engineer Dey's formulation based on Dey's patents. This provides a strong indication that the prior art provided Teva with no obvious alternative to Dey's invention.

e. Conclusion as to the Defense of Obviousness

There is no clear and convincing evidence that the scope and the content of the prior art included the motivation and capability to invent the patents-in-suit. Thus, the Asserted Claims are not invalid due to obviousness.

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C. Enablement

1. Standard of Law

A patent is invalid if it violates the enablement clause of 35 U.S.C. § 112. Section 112 demands that the patent enable others to replicate it. *Id.* Thus, a valid patent must disclose enough detail to enable a person of ordinary skill in the art to practice the invention “without undue experimentation at the time of filing.” Alza Corp. v. Andrx Pharms., LLC, 603 F.3d 935, 939 (Fed. Cir. 2010). The key word is ‘undue,’ not ‘experimentation.’ *Id.* Accordingly, patents need not be exact blueprints for commercial production of a product.

2. Findings of Fact and Conclusions of Law

Teva challenges whether the First Family patents “teach those in the art enough that they can make and use the invention without undue” experimentation.¹⁰ Amgen Inc. v. Hoeschst Marion Roussel, Inc., 314 F.3d 1313, 1335 (Fed. Cir. 2003). Teva focuses its enablement argument on several claims of the ‘355 and ‘953

¹⁰Teva’s main focus at trial was on the defenses of anticipation and obviousness. Its argument regarding the affirmative defense of enablement appears only briefly in its post-trial briefs.

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Patents,¹¹ contending that they do not teach a person of ordinary skill in the art the specific buffers and pH range needed to practice the invention. (Dkt. No. 249).

Teva's argument that the specifications of the First Family patents are non-enabling is unavailing. First, the required level of skill in the art is high. As the Court has determined, a person of ordinary skill in the art is an individual with an advanced degree in Pharmacy with experience in creating pharmaceutical formulations. Secondly, the patents-in-suit provide sufficient guidance that such a skilled artisan could practice the claimed invention. The specifications in the First Family patents disclose experimental data illustrating that formoterol is most stable, and therefore suitable for long-term storage, within the range of pH 4.0 to 6.0. The Patents specify that "[t]he rate constant...at a pH of 3, 4, 5, and 7 is approximately 0.62, 0.11, 0.044, and 0.55, respectively. Therefore, the decomposition of formoterol...is slowest at a pH of about 5.0." (TX 1, 9:24-41). A person of ordinary skill in the art would credit this teaching and have no reason to engage in "undue experimentation" with pH solutions

¹¹These claims include claims 3, 34, 40, 65, 74, 104 and 116 of the '344 Patent and claims 76, 106, 112, 136, and 160 of the '953 Patent.

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outside this range. The specifications further teach that suitable buffers include citrate, phosphate, and acetate (TX 1, 10:9-13), which are known to control pH within the range of 4.0 to 6.0. (Tr. 581:5-13 (Myrdal).)

Teva also contends that various claims of the First Family Patents are not enabled because their specifications include a list of several buffers, three of which a person of ordinary skill in the art would not consider suitable for buffering an inhalation solution. (Dkt. No. 249). However, only two non-asserted claims include the full list of suitable buffers.¹² All of the Asserted Claims either specify the use of a citrate buffer or do not call for the use of any specific buffer. Thus, Teva's argument that the buffers of the Asserted Claims are not enabled is without merit.

Teva further contends that various claims of the First Family Patents are not enabled because they recite a wide pH range of 2.0 to 8.0, thus preventing a person of ordinary skill in the art from identifying an appropriate pH range for the invention. However, of the claims Teva cites,¹³ only one of those claims includes a pH

¹²These claims include claim 11 of the '344 Patent and claim 83 of the '953 Patent.

¹³Id.

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limitation,¹⁴ and that claim recites a narrow pH range of 4.0 to 6.0. The rest of the claims do not require a pH limitation, but only solutions that are "suitable for" or "stable during long-term storage."

Thus, based on the above-cited specifications, a person of ordinary skill in the art would be able to conclude, without undue experimentation, that solutions "suitable for long-term storage" would have a pH in the range of 4.0-6.0, and that buffers useful to achieve such a pH would include citrate, acetate, and phosphate.

a. Conclusion as to Defense of Enablement

Teva has not demonstrated by clear and convincing evidence that the patents-in-suit fail the disclosure requirements set forth in 35 U.S.C. § 112.

VI. CONCLUSION

Teva has failed to prove, by clear and convincing evidence, that the Asserted Claims are invalidated by the doctrines of anticipation, obviousness, or enablement. In light of its prior findings of Teva's infringement, the Court **DECLARES** that the making, using, selling, offering to sell, or importing the inhalation product described in ANDA No. 91-141 constitutes

¹⁴This describes claim 160 of the '953 Patent.

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infringement of the patents-in-suit, and **ENJOINS** Teva, its officers, agents, servants and employees, from making, using, offering to sell, selling or importing the inhalation product described in ANDA No. 91-141. The Court also **ORDERS** that the effective date of the products described in ANDA No. 91-141 shall not precede the expiration of the patents-in-suit. Further, the Court **DENIES AS MOOT** all pending motions and **ORDERS** that this case be **DISMISSED WITH PREJUDICE** and be removed from its active docket.

It is so **ORDERED**.

Pursuant to Fed. R. Civ. P. 58, the Court directs the Clerk of Court to enter a separate judgment order and to transmit copies of both orders to counsel of record and all appropriate agencies.

Dated: March 21, 2014.

/s/ Irene M. Keeley
IRENE M. KEELEY
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

DEY, L.P., and DEY, INC.,

Plaintiffs,

v. // CIVIL ACTION NO. 1:09CV87
(Judge Keeley)

TEVA PARENTERAL MEDICINES, INC.,
TEVA PHARMACEUTICALS USA, INC., and
TEVA PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants.

MEMORANDUM OPINION AND ORDER CONSTRUING PATENT CLAIMS

This patent infringement case involves four United States Patents issued to the plaintiffs, Dey L.P. and Dey, Inc. ("Dey"), including 6,667,344 ("the '344 patent"), 6,814,953 ("the '953 patent"), 7,348,362 ("the '362 patent"), and 7,462,645 ("the '645 patent") (collectively, the "patents-in-suit"). The '344 and '953 patents, entitled "Bronchodilating Compositions and Methods," derive from provisional U.S. patent application 60/284,606, and share essentially identical specifications. The '362 and '645 patents, entitled "Bronchodilating Beta-Agonist Compositions and Methods," derive from provisional U.S. patent application 60/486,386. They too share essentially identical specifications that closely resemble those of the '344 and '953 patents.

The patents-in-suit cover aqueous compositions of formoterol, which allow the compositions to remain suitable for direct administration during long-term storage. They also cover methods

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for using these compositions to treat broncho-constrictive disorders. Dey uses the formulations and methods described in these patents in a commercial product known as Perforomist®.

I. BACKGROUND

In a letter dated May 12, 2009, the defendants, Teva Parenteral Medicines, Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceutical Industries, LTD. (collectively, "Teva"), notified Dey that they had filed an Abbreviated New Drug Application ("ANDA") seeking United States Food and Drug Administration ("FDA") approval to market a generic formoterol fumarate inhalation solution 0.02 mg/2mL ("generic formoterol fumarate product"). Teva also filed a certification with the FDA alleging certain claims of the four patents-in-suit are invalid, unenforceable and not infringed by Teva's manufacture or sale of its generic formoterol fumarate product. Dey in response filed this patent infringement action against Teva pursuant the Hatch-Waxman Act (the "Hatch-Waxman Act"). See 21 U.S.C. §§ 355, 360cc; 35 U.S.C. §§ 156, 271.

Dey contends that the product described in Teva's ANDA infringes claims in the four patents-in-suit, specifically claims 1-14, 16-22, 27-31, 33-39, 48, 61-62, 65, and 69-74 of the '344 patent, claims 1-13, 15-21, 26-30, 32-38, 58-63, 74-86, 90-94, 99-

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103, 105-111, and 131-136 of the '953 patent, claims 1-15 of the '362 patent, and claims 1-3, and 5-9 of the '645 patent (collectively, the "asserted claims").

The parties have identified four terms and phrases from the asserted claims in need of construction for which they have proposed competing claim constructions. They also have submitted six agreed claim constructions. Following a claims construction hearing on March 3, 2011, and after considering the parties' briefs and arguments, the Court adopts the following constructions.

II. LEGAL STANDARDS

The construction of patent claims presents a matter of law governed by federal statutes and the decisions of the Supreme Court of the United States and the United States Court of Appeals for the Federal Circuit. See Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995). When interpreting the meaning of a claim, a court may consider the claims, the specifications, and the prosecution histories as intrinsic evidence. Id. (quoting Unique Concepts, Inc. v. Brown, 939 F.2d 1558, 1561 (Fed. Cir. 1991)). According to a fundamental principle of claim construction, the invention itself, and the scope of a patentee's right of exclusion, will be defined by the patent's claims. See Phillips v. AWH Corporation, 415 F.3d 1303, 1312 (Fed. Cir. 2005)

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(en banc) (quoting Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1115 (Fed. Cir. 2004)); see also Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("[W]e look to the words of the claims themselves . . . to define the scope of the patented invention."). The description of an invention in the claims, therefore, limits the scope of the invention. Id.

Claim terms should be construed according to their "ordinary and customary" meaning, which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." Id. at 1313. Claim construction therefore requires a court to determine how a person of ordinary skill in the art would have understood the disputed term or phrase in question. "Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." Id.

When construing patent claims then, a court must consider the context of the entire patent, including both asserted and unasserted claims. Id. at 1314. Because a patent will ordinarily use patent terms consistently, "the usage of a term in one claim can often illuminate the meaning of the same term in other claims."

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Id. at 1314. Accordingly, "[d]ifferences among claims" can provide insight into "understanding the meaning of particular claim terms," and "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." Id. at 1314-15 (citing Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 910 (Fed. Cir. 2004)).

Aside from the claims themselves, the specification in the patent often provides the "'best source for understanding a technical term.'" Id. at 1315 (quoting Multiform Desiccants, Inc. v. Medzam, Ltd., 133 F.3d 1473, 1478 (Fed. Cir. 1998)). Pursuant to 35 U.S.C. § 112, ¶ 1, an inventor must use the specification to describe his claimed invention in "full, clear, concise, and exact terms." Accordingly, "[t]he claims of a patent are always to be read or interpreted in the light of its specifications." Schriber-Schroth Co. v. Cleveland Trust Co., 311 U.S. 211, 217 (1940).

An inventor may alter the "ordinary and customary" meaning of a term, however, by acting as his own lexicographer. This occurs, for example, when the patent specification defines a term in a manner different from its ordinary and customary meaning. Phillips, 415 F.3d at 1316. Thus, it is "entirely appropriate for a court, when conducting claim construction, to rely heavily on the

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written description for guidance as to the meaning of the claims."

Id. at 1317.

Nevertheless, a court may not import a limitation into the claims from the specification. Id. at 1323. Moreover, the Federal Circuit has "repeatedly warned" against limiting the claims to the embodiments specifically described in the specification. Id. In other words, a court should not construe the patent claims as being limited to a single embodiment simply because the patent describes only one embodiment. Id. (citing Gemstar-TV Guide Int'l Inc. v. Int'l Trade Comm'n, 383 F.3d 1352, 1366 (Fed. Cir. 2004)).

The prosecution history of a patent may also provide insight into the meaning of a term or phrase. "Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent." Id. at 1317. The inventor's limitation of the invention during the patent's prosecution may suggest that a claim has a narrower scope than it otherwise might have. Id.

Finally, when determining the ordinary and customary meaning of a term, a court must be cautious when considering extrinsic evidence, such as expert testimony, dictionaries, and learned treatises. Id. Nevertheless, such sources may be reliable if they were publicly available and show "what a person of skill in

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the art would have understood disputed claim language to mean.’’

Id. at 1314 (quoting Innova, 381 F.3d at 1116).

It is with these legal principles in mind that the Court turns to the construction of the four disputed terms or phrases among the asserted claims of the patents-in-suit.

III. ANALYSIS

A. “Formulated at a concentration suitable for direct administration”

Dey proposes that the phrase “formulated at a concentration suitable for direct administration,” as used in claim 1 of the ‘344 patent and claim 74 of the ‘953 patent means “ready to administer directly to a subject in need thereof, without mixing or diluting.”¹ Teva construes the phrase to mean “the composition is formulated at a concentration that is capable of being administered directly to a subject in need thereof.”

According to Dey, its proposed construction is supported by the claims, the specifications, the prosecution histories of the patents-in-suit, and the inventors’ sworn deposition testimony. It argues that Teva’s proposed construction improperly treats “capable

¹ Initially, Dey proposed the following construction: “ready to administer directly to a subject in need thereof, without mixing or diluting, at a free-base concentration of about 5 µg/mL to about 2mg/mL.” It has since, however, withdrawn the last phrase. See Transcript of Record at 10-11, Dey, et al. v. Teva, et al., No. 1:09CV87 (N.D.W. Va. Mar. 3, 2011) (dkt. no. 95).

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of" as a synonym for "suitable for." Teva claims that the intrinsic evidence supports its proposed construction, and that Dey has impermissibly added limitations that have no intrinsic basis.

1. The Claims

According to Dey, the claims themselves support its proposed construction because the ordinary meaning of the term "formulated" is "made, manufactured, devised, composed, produced, or fabricated." Pl.'s Opening Claim Construction Report at 5 (citing Cambridge Dictionary of American English 339 (Cambridge University Press 2000) (dkt. no. 69-5) (dkt. no. 69)). Teva, however, argues that the phrase "without mixing or diluting" in Dey's proposed construction improperly shifts the claim's focus from the time of the composition's manufacture to the time after formulation, which Teva contends is irrelevant to "whether the composition was 'formulated at a concentration suitable for direct administration.'" Def.'s Rebuttal Report at 10 (dkt. no. 76). Teva also argues that Dey's construction renders the claims indefinite because a person of ordinary skill in the art could only know if another composition infringed Dey's composition by discovering how the composition is used. See IPXL Holdings, L.L.C. v. Amazon.com, Inc., 430 F.3d 1377, 1384 (Fed. Cir. 2005) (holding that a claim is invalid when it is indefinite and fails to "apprise

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a person of ordinary skill in the art of its scope").

Dey denies that its proposed construction focuses on what happens to a composition after its formulation, claiming it clarifies how a composition must be created or made in order to be "suitable for direct administration." It contends that a composition is created or made to be "suitable for direct administration" when it is "ready to administer" without the need for "mixing or diluting."

The claims themselves, unfortunately, fail to shed sufficient light on the meaning of this requirement. The Court therefore must look beyond the claims to the specifications and prosecution histories of the patents-in-suit to construe this phrase.

2. The Specifications

According to Dey, the specifications provide intrinsic support for its proposed construction. A specification may define a claim term explicitly or by implication. Astrazeneca AB, Aktiebolaget Hassle, KBI-E, Inc. v. Mutual Pharm. Co., Inc., 384 F.3d 1333, 1339-40 (Fed. Cir. 2004). Moreover, "[w]here the general summary or description of the invention describes a feature of the invention . . . and criticizes other products . . . that lack that same feature, this operates as a clear disavowal of these other products[.]" Id. In any event, "the claims cannot be of broader

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scope than the invention that is set forth in the specification."

On Demand Machine Corp. v. Ingram Industries, Inc., 442 F.3d 1331, 1340 (Fed. Cir. 2006).

Here, the specifications describe the prior art of Hochrainer in U.S. Patent No. 6,150,418 ("Hochrainer") as:

a "liquid active substance concentrate" containing formoterol in the form of its free base, or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as active substance.

'344, col. 7, ll. 65-67, col. 8., ll. 1-2. They also describe Hochrainer's formoterol concentrate as unsuitable for direct administration:

The specification [of Hochrainer] provides . . . that it is the high concentration that allows for the stability of the concentrate. **The "liquid active substance concentrate" is not suitable for direct administration to a patient.**

Id. at col. 8, ll. 7-10 (emphasis added).

In contrast, the specifications in the '344 and '953 patents expressly provide that Dey's compositions are "suitable for direct administration to a subject in need thereof." Id. at col. 2, ll. 24-29; '953, col 2, ll. 35-37. Dey argues that this distinction provides helpful insight for determining what a person of ordinary skill in the art would understand the phrase "suitable for direct

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administration" to mean. See Arthur A. Collins, Inc. v. Northern Telecom Limited, 216 F.3d 1042, 1045 (Fed. Cir. 2000) (recognizing that a patentee's citation to the prior art can provide helpful guidance for determining a claim term's meaning to a person of ordinary skill in the art).

The specification in Hochrainer provides that "[t]he active substance concentrate according to the invention may be converted, by **diluting** with a pharmacologically acceptable liquid." Hochrainer, col. 1, ll. 47-49 (emphasis added). It clarifies that "'highly concentrated'" means "a concentration of the active substance which is usually too high to enable the corresponding solution or suspension to be used therapeutically for inhalation **without being diluted**." Id. at col. 2, ll. 1-4 (emphasis added).

Hochrainer also provides that "[t]he active substance concentrate according to the invention is **not** usually **suitable** as such for **direct** medicinal use," and that "[a] preferred method of converting the active substance concentrate into a **pharmaceutical preparation suitable for administration** is by **diluting** the active substance concentrate according to the invention with a pharmacologically suitable solvent or suspension agent." Id. at col. 4, ll. 9-11, 21-25. It also repeatedly provides that the active substance concentrate may be diluted by mixing it with a

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"diluent." See id. at col. 5, ll. 1-5, 20-27, 42-45, 57-67, col. 6, ll. 16-21.

These properties establish that the inventors of Dey's compositions viewed Hochrainer's formoterol concentrate as unsuitable for direct administration because it usually needed to be mixed with a diluent prior to administration to a patient. Dey argues to persuasive effect that, because the '344 and '953 patents distinguish themselves from Hochrainer based on their suitability for direct administration, a person of ordinary skill in the art would understand that a composition is "formulated at a concentration suitable for direct administration" when it is "ready to administer directly to a subject in need thereof, without mixing or diluting."

3. The Prosecution Histories

Beyond the specifications and prior art, further support for Dey's proposed construction can be found in the prosecution histories of the patents-in-suit. See Ormco Corporation v. Align Technology, Inc., 498 F.3d 1307, 1314 (Fed. Cir. 2007). "Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent." Phillips, 415 F.3d at 1317; see also Sentry Prods., Inc. v. Eagle Mfg. Co., 400 F.3d 910, 915 (Fed. Cir. 2005) (holding that the prosecution history may

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comprises water, and the composition is
**formulated at a concentration suitable
for direct administration to a subject in
need thereof.**

Dey, Amendment at 2 (June 22, 2001) (dkt. no. 69-8) (emphasis added).

1. (Amended) A kit, comprising:
 - (a) an aqueous composition comprising formoterol or a derivative thereof
formulated at a concentration suitable for direct administration to a subject in need thereof, wherein the composition is stable during long term storage; and
 - (b) a nebulizer.

Dey, Amendment at 1 (May 3, 2002) (dkt. no. 69-12) (emphasis added).

At the time it submitted its amended version of claim 1 for the '344 patent, Dey also stated:

Hochrainer et al. discloses that it is the high concentration that allows for the stability of the concentrate. The **cited reference does not disclose stable, aqueous compositions** containing formoterol **formulated at a concentration for direct administration to a subject in need thereof, as required by the instantly-claimed compositions.**

The "highly concentrated" **"active substance concentrate"** of the reference is **not suitable for direct administration** to a subject in need thereof.

. . . .

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Thus, the "active substance concentrate" of Hochrainer et al. is merely a means for the storage of highly concentrated solutions of formoterol, and is not formulated at a concentration for direct administration to a subject in need thereof.

Dey, Amendment at 14-15 (June 22, 2001) (dkt. no. 69-8) (emphasis added) (prosecution history for the '344 patent) (dkt. no. 69-8). Dey provided a similar response to the U.S. Patent and Trademark Office following rejection of the '953 patent application. Dey, Amendment at 8-10 (May 3, 2002) (dkt. no. 69-12) (prosecution history of the '953 patent). After receiving these responses, the examiners at the U.S. Patent and Trademark Office approved Dey's amended claims.

Dey supported its construction during the claims construction hearing by analogizing Hochrainer's formoterol concentrate to frozen orange juice concentrate that must be mixed or diluted with water prior to being suitable for drinking. Dey then compared its own compositions to orange juice that may be consumed directly from a bottle, without the need for mixing or diluting. See Transcript of Record at 18, Dey, et al. v. Teva, et al., No. 1:09CV87 (N.D.W. Va. Mar. 3, 2011) (dkt. no. 95). Dey contended that it is this vital difference that renders its compositions of formoterol "suitable for direct administration" and therefore "ready to use."

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In response to this analogy, Teva pointed out that people commonly mix orange juice with vodka prior to consuming it. Id. at 73. According to Teva, vodka is suitable for direct consumption regardless of whether a person later mixes or dilutes it with orange juice, and because of this the phrase "suitable for direct administration" would not preclude an end user from further diluting or mixing Dey's compositions. According to Teva, Dey's focus on how the compositions must be used prior to administration renders the patents indefinite. See IPXL Holdings, 430 F.3d at 1384.

While Teva is correct that the construction of the phrase "formulated at a concentration suitable for direct administration" does not hinge on what happens to the compositions after formulation, its argument is ultimately unpersuasive. The disputed phrase begins with the term "formulated," and there is no indication in the intrinsic evidence that Dey modified the ordinary meaning of this term, which commonly means "created."² See Phillips, 415 F.3d at 1314 (citing Brown v. 3M, 265 F.3d 1349, 1352 (Fed. Cir. 2001) (recognizing that claim meaning will sometimes be "readily apparent even to lay judges," and that "claim construction

² See also Cambridge Dictionary of American English 339 (Cambridge University Press 2000) (defining "formulated") (dkt. no. 69-5).

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in such cases involves little more than the application of the widely accepted meaning of commonly understood words."). In point of fact, the term "formulated" in the disputed phrase clarifies that suitability for "direct administration" turns on how the compositions must be created. Once the compositions are formulated in a way that renders them "suitable for direct administration," it is irrelevant to the analysis what may happen to them afterward. Stated another way, the phrase "formulated at a concentration suitable for direct administration" does not restrict usage of the compositions after formulation but rather provides a guidepost for how the compositions must be "formulated."

Given that, the question becomes what properties and characteristics must the compositions possess in order to be "formulated at a concentration suitable for direct administration?" The repeated disavowal in the intrinsic evidence of the "active substance concentrate" of Hochrainer persuades the Court that Dey's compositions are "suitable for direct administration" because, unlike the prior art of Hochrainer's concentrate, they are "formulated" at a concentration that renders it unnecessary to mix or dilute them prior to administration. Thus, they are "ready to use" in the same way that liquid orange juice is "ready to use," without diluting or mixing prior to consumption. Once formulated,

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it is irrelevant to Dey's compositions whether an end user mixes or dilutes them further because it is at the time of manufacture that they must be "ready to administer, without mixing or diluting."

Teva's proposed construction not only lacks evidentiary support, it also is not consistent with the intrinsic evidence. At bottom, it substitutes "capable of" for "suitable for." Under that construction, the concentrate in Hochrainer also would be "capable of" direct administration because it could be so administered after mixing or dilution. Teva's construction, thus, fails to reconcile Dey's important disavowal of Hochrainer's formoterol concentrate in the intrinsic evidence, and conflicts with what a person of ordinary skill in the art would understand the disputed phrase to mean.

In conclusion, although "ready to administer directly" and "without mixing or diluting" do not appear in either the '344 or '953 patents, the specifications and prosecution histories of these patents establish that a person of ordinary skill in the art would understand the phrase "formulated at a concentration suitable for direct administration" to mean that the compositions must be "ready to use," and that the compositions are "ready to use" when they can be administered without diluting or mixing. See Ormco, 498 F.3d at 1314. The Court therefore adopts Dey's proposed construction

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that a composition is "formulated at a concentration suitable for direct administration" when it is "ready to administer directly to a subject in need thereof, without mixing or diluting."³

B. "Pharmaceutical composition"

Dey construes the term "pharmaceutical composition," as used in claim 1 of the '344 patent, claim 74 of the '953 patent, claim 1 of the '362 patent, and claim 1 of the '645 patent, to mean "a medicinal formulation containing an active drug and inert excipients." Teva construes it to mean "a stable composition."

Dey argues that the intrinsic evidence does not change or modify the plain and ordinary meaning of "pharmaceutical composition," and that Teva's proposed construction inappropriately seeks to construe a preamble phrase. While Teva does not dispute that Dey's construction is the plain and ordinary meaning of the term, it claims the intrinsic evidence of the patents-in-suit establish that the inventors modified that meaning to include only compositions that are themselves intrinsically stable. Further, it argues the term constitutes a necessary antecedent that provides

³ Because the Court adopts Dey's proposed construction, it need not consider the testimony of the inventors. See Howmedica Osteonics Corp. v. Wright Med. Tech., Inc., 540 F.3d 1337, 1346-47 (Fed. Cir. 2008) (recognizing that consideration of inventor testimony is often inappropriate and unnecessary during claim construction).

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structure for subsequent claim terms.

There is a “‘heavy presumption’ that a claim term carries its ordinary and customary meaning.” CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1366 (Fed. Cir. 2002). This presumption does not apply, however, where “the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in either the specification or prosecution history.” Id. (citing Johnson Worldwide Associates, Inc. v. Zebco Corp., 175 F.3d at 990 (Fed. Cir. 1999)). To determine whether a disputed term has a definition different from its ordinary and customary meaning, courts may consider the claims, the specification, and the prosecution history. See Bell Atlantic Network Services, Inc. v. Covad Communications Group, Inc., 262 F.3d 1258, 1268-69 (Fed. Cir. 2001).

1. The Claims

According to Teva, the term “pharmaceutical composition” provides a claim limitation of overarching stability that is distinct from the mere requirements of stability “during long term storage” and “shelf life.” Dey argues that this construction imports an unwarranted “stability” limitation where the term “stable” appears in the claims only in conjunction with the phrase “stable during long term storage.” Further, because

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"pharmaceutical composition" appears in preamble phrases, Dey contends it is a general term that does not limit the scope of the claims. Finally, Dey asserts the claims themselves support its construction of a "pharmaceutical composition" comprising an active drug, formoterol, and inert excipients, including a polar solvent, a tonicity adjusting agent, and a buffer. See, e.g., '344, cls. 1, 5, 7, 10.

Generally, "'the preamble does not limit the claims.'" See Am. Med. Sys., Inc. v. Biolitec, Inc., 618 F.3d 1354 (Fed. Cir. Sept. 13, 2010) (quoting Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1346 (Fed. Cir. 2002)). Therefore, to determine whether a preamble constitutes a substantive limitation, a court must evaluate the entire patent in order to understand the scope of the invention and the inventors' intent as to the meaning and scope of the claims. See Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 808 (Fed. Cir. 2002) (quoting Corning Glass Works v. Sumitomo Electric U.S.A., Inc., 868 F.2d 1251, 1257 (Fed. Cir. 1989)).

A preamble phrase does not constitute a substantive limitation when it states the invention's "purpose or intended use," and the body of the claim completely defines the claimed invention. Id.; see also Biolitec, 299 F.3d at 1346 (quoting

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Catalina, 289 F.3d at 809) (holding that “[a] preamble is not regarded as limiting . . . ‘[w]hen the claim body describes a structurally complete invention such that deletion of the preamble phrase does not affect the structure or steps of the claimed invention.’”). Nor does it constitute a substantive limitation when by using a “descriptive name” it identifies a complete invention set forth in the body of the claims. Id. (quoting IMS Tech., Inc. v. Haas Automation, Inc., 206 F.3d 1422, 1434-35 (Fed. Cir. 2000)). However, a phrase does constitute a substantive limitation if it includes “essential structure or steps, or if it is ‘necessary to give life, meaning, and vitality’ to the claim.” Catalina, 289 F.3d at 808 (quoting Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1309 (Fed. Cir. 1999)).

In the patents-in-suit, the term “pharmaceutical composition” appears both as preamble phrases and also in the body of the claims. For example, the ‘344 patent describes a “pharmaceutical composition” as being comprised of:

1. . . . formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof.

‘344, cl. 1 (emphasis added) (preamble). Similarly, the ‘953

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patent describes

[a] method for the treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, comprising administering an effective amount of a pharmaceutical composition to a subject in need of such treatment, wherein the **pharmaceutical composition** comprises formoterol or a derivative thereof formulated at a concentration suitable for direct administration to a subject in need thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage and the fluid comprises water.

'953, cl. 74 (emphasis added) (body). Thus, to resolve whether the term "pharmaceutical composition" constitutes a "life-giving" limitation or a non-limiting and general description, the Court must review the patent as a whole. See Catalina, 289 F.3d at 808.

2. The Specifications

Teva contends the specifications only describe pharmaceutical compositions that are themselves intrinsically stable. Further, it contends that the specifications contrast the prior art of Hochrainer to Dey's compositions based on stability, and also describe the other formulation excipients based on their stability as well.

In pertinent part, the specifications state that

[t]he compositions provided herein are **stable** solutions of a bronchodilating agent, or a derivative thereof, in a pharmacologically

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suitable fluid that contains water, that are
stable during long term storage.

'344, col. 2, ll. 23-28 (emphasis added); '953, col. 2, ll. 32-35 (emphasis added). It is precisely because the specifications provide that the compositions are "stable" and "stable during long term storage" that Teva argues the term "pharmaceutical composition," as used in the patents-in-suit, includes an overarching requirement of stability distinct from the requirement of merely being "stable during long term storage." It also contends that the specifications themselves define this overarching requirement of stability:

As used herein, the stability of a composition provided herein refers to the length of time at a given temperature that is greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient, e.g., formoterol, is present in the composition. Thus, for example, a composition that is stable for 30 days at 25° C. would have greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient present in the composition at 30 days following storage at 25° C.

'344, col. 5, ll. 30-38; '953, col. 5, ll. 40-48.

While Dey agrees that the compositions must be "stable," it argues that this characteristic derives from the requirement that the compositions be "suitable for direct administration." According to Dey, "stability" is not a characteristic that is inherent in the term "pharmaceutical composition." It contends the

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term itself implies no limitation of stability, and only appears in the claims as a general term. Dey also contends that Teva's suggested requirement of overarching stability fails to illuminate the term's meaning because the patents-in-suit do not establish durations or temperature limits for measuring it. Absent such context, Teva's stability requirement is meaningless in Dey's view.

After careful consideration of the specifications, the Court concludes that the inventors did not define "pharmaceutical composition" to mean a "stable composition" with the reasonable clarity, deliberateness, and precision required when an inventor applies his own lexicography to a claim term. See In re Paulson, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Whether it appears in the preamble of some claims, or in the body of others, the term provides only the general context of the inventions, not a substantive limitation. Compare '344, cl. 1 (preamble) with '953, cl. 74 (body).

3. The Prosecution Histories

The prosecution histories of the patents-in-suit further undermine Teva's proposed construction. Teva contends that during the prosecution of the patents Dey argued that the "stability" of its compositions distinguished them from the prior art because Hochrainer "does not disclose stable, aqueous compositions

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containing formoterol[.]” Dey, Amendment at 14 (June 22, 2001) (dkt. no. 69-8) (*‘344 prosecution history*).

Teva’s emphasis on this excerpt from the prosecution history ignores the full context of Dey’s argument, which includes the following:

The cited reference does not disclose stable, aqueous compositions containing formoterol formulated at a concentration for direct administration to a subject in need thereof, as required by the instantly-claimed compositions.

Id. (emphasis added). Tellingly, as to the *‘344* patent, Dey never distinguished its compositions from the prior art based on stability alone, but relied on stability coupled with suitability for direct administration. Dey also made this same distinction during the prosecution of the *‘953* patent. *See* Dey, Amendment (May 3, 2002) (dkt. no. 69-12) (*‘953 prosecution history*).

While prosecuting the *‘362* patent, Dey acknowledged that Hochrainer’s concentrations were stable, but distinguished its own compositions based on characteristics of stability coupled with their suitability “for direct administration.” Dey, Amendment (July 9, 2004) (dkt. no. 68-14) (*‘362 prosecution history*); *see also* Dey, Amendment at 12 (Mar. 23, 2007) (dkt. no. 71) (stating that, unlike the prior art of Hochrainer, the compositions of the

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'362 patent would be stable during long term storage and be "ready-to-use"). Dey never asserted that its pharmaceutical compositions had an inherent characteristic of "stability" distinct from being "stable during long term storage."

The prosecution histories, thus, fail to support Teva's argument. The term "pharmaceutical composition" is a general one, and, as discussed, none of the intrinsic evidence supports a construction otherwise. The Court therefore adopts Dey's proposed construction that the term "pharmaceutical composition" means "a medicinal formulation containing an active drug and inert excipients."

C. "Shelf life"

Dey construes the term "shelf life," as used in claim 2 of the '344 patent, claims 2 and 75 of the '953 patents, claims 1-3 and 9-10 of the '362 patents, and claims 2-3 of the '645 patent, to mean "the period of time during which a drug may be stored and remains suitable for use."⁴ It points out that certain claims require the

⁴ The '344 and '953 patents use the term "shelf-life," while the '362 and '645 patents use the term "shelf life." Compare '344 patent, cl. 2; '953 patent, cl. 2 with '362 patent, cl. 1; '645 patent, cl. 2. This opinion will use the preferred dictionary form of the term, "shelf life." See, e.g., Merriam-Webster's Third International Dictionary, Unabridged 2092 (Merriam-Webster, Inc., 3d ed. 2002); Merriam-Webster's Medical Desk Dictionary 740 (Merriam-Webster, Inc., 1996).

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compositions to exhibit adequate "shelf life," see '344 patent, cl. 2; '953 patent, cl. 75, and refutes Teva's contention that, because the claims themselves state the shelf life durations of the compositions, those durations define the term. See '344, cl. 2 (stating that "the composition has an estimated shelf[]life of greater than 1 month usage time at 25° C and greater than or equal to 1 year storage time at 5° C."); '953, cls. 2, 75 (same); '362 Patent, cl. 1 (stating that the composition has "an estimated shelf life of greater than 90% after 3 months storage at 25° C and after 3 years storage at 5° C.").

Relying on Merriam-Webster's Medical Desk Dictionary, Dey asserts that the ordinary meaning of "shelf life" is "the period of time during which a material (as a food or drug) may be stored and remains suitable for use." Merriam-Webster's Medical Desk Dictionary 740 (Merriam-Webster, Inc., 1996). It further asserts that neither the claims, specifications, nor the prosecution histories of the patents-in-suit modify this common definition.

Notably, Teva does not propose a construction for the term "shelf life." Rather, pointing to the claims, it argues that reliance on a dictionary definition is improper because the claims themselves provide the definition. See TAP Pharm. Prods., Inc. v. Owl Pharm., L.L.C., 419 F.3d 1346, 1354 (Fed. Cir. 2005) (reasoning

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that "a word describing patented technology takes its definition from the context in which it was used by the inventor."). Teva also asserts that Dey is seeking to have the Court rewrite, not merely interpret, the plain language of the claims. For example, as to claim 2 of the '344 patent, it contends that the shelf life durations of 1 month usage time at 25° C, and greater than or equal to 1 year storage time at 5° C, constitute distinct requirements, which Dey's proposed construction improperly conflates by "requiring that the composition be stored and remain suitable for use for more than 1 month usage time at 25° C and at least 1 year at 5° C[.]" Def.'s Rebuttal Brief at 20 (dkt. no. 76).

The interpretation of a claim's meaning begins with how a person of ordinary skill in the art would understand it. See Phillips, 415 F.3d at 1313 (citations omitted). While extrinsic sources, such as technical dictionaries, can provide a court with an educational resource for determining how a person of ordinary skill in the art would understand a claim term or phrase, such sources are inherently less reliable than the intrinsic evidence. Id. at 1319. Thus, a court may never use a dictionary definition to alter the meaning of a claim provided by an intrinsic source. Id.; see also C.R. Bard, 388 F.3d at 862. When construing a commonly used term, however, a court may sometimes construe it by

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applying its "widely accepted meaning." Phillips, 415 F.3d at 1314 (citing Brown v. 3M, 265 F.3d 1349, 1352 (Fed. Cir. 2001)).

Teva's contentions, that, first, the Court need not construe the term because the claims and specifications already define it, and, second, the definition of "shelf life" has separate requirements for "usage time" and "storage time" which Dey merges into one, are unavailing. The argument that the "shelf life" durations for "storage time" and "usage time" constitute distinct requirements fails to explain why these terms are distinct or why these purported distinctions are significant. Moreover, while contending that the Court need not construe the term, Teva fails to explain how the "shelf life" durations on which it relies define it.

On this issue, the intrinsic evidence, unfortunately, is not helpful. Dey's construction, even though based on an extrinsic source, a medical dictionary, does provide a common definition establishing the significance of the "shelf life" durations cited by Teva, while neither modifying nor contradicting the intrinsic evidence. Its proposed construction also establishes that a composition stored at "5° C" for "1, 2 or 3 years," see '344 patent, col. 6, ll. 66-67, col. 7, ll. 1-4, would remain suitable for use, a fact that could not otherwise be determined if the Court

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does not construe the term. Dey's construction of "shelf life," thus, is both consistent with the intrinsic evidence and also clarifies the significance of the "shelf life" durations. The Court therefore concludes that "shelf life" means "the period of time during which a drug may be stored and remains suitable for use."

D. "Formulated for single dosage administration"

Dey construes the phrase "formulated for single dosage administration," as used in claims 62, and 65 of the '344 patent, to mean "formulated in a quantity that is taken or administered at one time." Teva's construction is "the formoterol fumarate is formulated for single dosage administration via nebulization at a concentration of about 100 µg/mL." Neither party's arguments are grounded substantially in the intrinsic evidence; Teva relies exclusively on a single embodiment found in the specification, while Dey relies on extrinsic evidence to interpret the specification's examples and construe the disputed phrase.

1. The Claims

Dey points out that Teva's construction would render claim 66 of the '344 patent internally inconsistent, and therefore invalid, because it would require a composition "formulated for single dosage administration" to have a formoterol concentration of "about

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description.”⁵ Rhine v. Casio, Inc., 183 F.3d 1342, 1345 (Fed. Cir. 1999).

The Federal Circuit instructs that “claims are generally construed so as to sustain their validity, if possible.” Whittaker Corp. by Technibilt Div. v. UNR Industries, Inc., 911 F.2d 709, 711-12 (Fed. Cir. 1990) (citing ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577 (Fed. Cir.1984)). This axiom only applies, however, when a claim’s construction is consistent with the claim’s language and the written description. Rhine, 183 F.3d at 1345. In other words, a court may not rewrite a claim to preserve its validity. Id. (citing Becton Dickinson & Co. v. C.R. Bard, Inc., 922 F.2d 792, 799 & n.6 (Fed. Cir. 1990)). Here, because the claims themselves provide little insight into the meaning of the disputed phrase, the Court must examine the specification to determine whether it explicitly defines “formulated for single dosage administration” as urged by Teva.

2. The Specification

Dey relies on extrinsic sources to argue that examples from the specification support its construction that “formulated for

⁵ As discussed earlier, although Dey does not assert claim 66, the Federal Circuit has instructed that “both asserted and unasserted [claims] can . . . be valuable sources of enlightenment as to the meaning of a claim term.” Phillips, 415 F.3d at 1314.

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single dosage administration" means "formulated in a quantity that is taken or administered at one time." It points out that examples one and two disclose formulations with the same proportional concentrations of formoterol but different solution quantities. It then relies on extrinsic sources to establish that example two discloses "single use" formulations, and that this example establishes that formulation for "single dosage administration" turns on solution quantity, not a specific concentration of formoterol. Teva, on the other hand, argues simply that the specification provides an express definition for the disputed phrase because the only embodiment with a composition "formulated for single dosage administration" has a formoterol concentration of "about 100 µg/mL."

Dey points out that example one in the '344 patent describes two preparations of formoterol using a solution quantity of two liters of purified water: a "low dosage strength" formulation with a formoterol concentration of 85 µg/mL, and a "high dosage strength" formulation with a formoterol concentration of 170 µg/mL.⁶ See '344, Example 1. It refers to these preparations as

⁶ Example one describes the "low dosage strength" formulation as having 0.17 g of formoterol in two liters of water: 0.17 g formoterol / 2 L water = 0.085 g/L = 85 µg/mL. Example two also describes the "high dosage strength" formulation as having 0.34 g of formoterol in two liters of water: 0.34 g formoterol / 2 L water

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"bulk" formulations.

Like its "bulk" formulation counterparts, example two of the '344 patent describes "unit dose" formulations with "low strength" and "high strength" formulations that have the same proportional formoterol concentrations as the formulations in example one: 85 µg/mL, and 170 µg/mL, respectively.⁷ *Id.* at Example 2. Unlike the two liters of purified water needed for the "bulk" formulations, however, the "unit dose" formulations are prepared with the far smaller quantity of two milliliters of purified water.⁸

Because the specification does not define the term "unit dose," or provide additional insight into its meaning, Dey relies on an extrinsic source, the FDA Compliance Policy Guide, § 430.100 (1984) (dkt. no. 77-2), to establish that a "unit dose" is a "single dose." Further, relying on the Merriam-Webster's Medical Dictionary 218 (Merriam-Webster, Inc., 1996) (dkt. no. 69-19), it contends that a "dose" is "the measured quantity of a therapeutic

= 0.17 g/L = 170 µg/mL.

⁷ Example two describes the "low strength" unit dose as having 0.017 mg of formoterol in two milliliters of water: 0.17 mg formoterol / 2 mL water = 0.085 mg/mL = 85 µg/mL. Example two also describes the "high strength" unit dose as having 0.34 mg of formoterol in two milliliters of water: 0.34 mg formoterol / 2 mL water = 0.17 mg/mL = 170 µg/mL.

⁸ 2,000 milliliters = 2 liters.

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agent to be taken at one time." From these sources, Dey concludes that the "unit dose" formulations of example two are "single doses" that are "formulated for single dosage administration" because they are "formulated in a quantity that is taken or administered at one time."

Citing to Vitronics Corp. v. Conceptronic, Inc., Teva contends that Dey's reliance on extrinsic sources is improper because the specification provides an express definition that contradicts Dey's construction. 90 F.3d at 1582. In Vitronics, the Federal Circuit observed that the plaintiff's construction would prevent the specification's only embodiment from being covered by the claims. Id. at 1583. Given that "[s]uch an interpretation is rarely, if ever, correct," and can only be sustained with "highly persuasive evidence," the Federal Circuit rejected that construction, holding that the district court had relied improperly on extrinsic evidence providing a conflicting interpretation. Id.

In contrast to the construction in Vitronics, Dey's construction here is consistent with the specification's embodiments and claims, while Teva's construction would render claim 66, which is "formulated for single dosage administration," internally inconsistent and invalid since it obviously cannot have a formoterol concentrate of "59 µg/mL" and "100 µg/mL." See '344

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patent, cls. 66, 53, 42. As discussed below, Teva fails to establish that the embodiment it cites defines the disputed phrase. Dey's construction, moreover, is consistent with the specification and would preserve the validity of claim 66.

Although extrinsic evidence is disfavored and often unreliable, a district court is not forbidden from relying on it in all cases. For example, in the landmark case of Phillips, the Federal Circuit, sitting en banc, recognized that extrinsic evidence may be helpful in determining a "reliable interpretation of patent claim scope" when it is "considered in the context of the intrinsic evidence." 415 F.3d at 1319. Thus, within the context of the intrinsic evidence, a district court may rely on extrinsic sources to educate itself "regarding the field of the invention," or to determine what a person of ordinary skill in the art would understand claim terms to mean. Id.

While an extrinsic source may never be used to contradict intrinsic evidence, the FDA Compliance Policy Guide relied on by Dey evinces a "commonly understood meaning" of the term "unit dose" that also comports with the intrinsic evidence. See id. at 1319, 1321. Therefore, when the definition of "unit dose" as a "single dose" is considered within the context of the specification and the claims as a whole, there being no intrinsic or extrinsic evidence

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to the contrary, the Court concludes that Dey's reliance on an extrinsic source to define the "unit dose" formulations of example two as constituting "single dose" formulations is justified.

Defining "unit dose" as a "single dose," however, does not resolve whether "single dose" means "single dosage." "Dose" and "dosage" have distinct, yet similar, meanings. According to Merriam-Webster's Third International Dictionary, Unabridged 676 (Merriam-Webster, Inc., 3d ed. 2002), a "dose" is "the measured quantity of a medicine or other therapeutic agent to be taken at one time or in a period of time," while "dosage" is "the amount of medicine or other therapeutic agent . . . prescribed or proper for a given patient or illness." Despite subtle differences, a "single dosage" reasonably may be understood as an amount of medicine prescribed to be taken or administered at one time-- that is, a "dose." In this context, the Court finds no meaningful distinctions between the ordinary meaning of the terms "single dose" and "single dosage."

Given the lack of a meaningful distinction between the terms, and given that the defining feature of the "unit dose" formulations in example two is solution quantity, Dey's proposed construction, that formulation "for single dosage administration" turns on a solution quantity to be taken or administered at one time, and not

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establish that Dey expressed a clear intent to define formulation "for single dosage administration" on the basis of a formoterol concentration of "about 100 µg/mL." Although the only embodiment in the specification disclosed as being "formulated for single dosage administration" has a formoterol concentration of "about 100 µg/mL," the specification includes no "'words or expressions of manifest exclusion or restriction'" establishing Dey's intent to limit and define the phrase as Teva construes it. I4I Limited Partnership, 598 F.3d at 843 (quoting Liebel-Flarsheim, 358 F.3d at 907-08). To the contrary, the specification is ambiguous on this issue; it neither states nor implies that all compositions "formulated for single dosage administration" must have a formoterol concentration of "about 100 µg/mL."

Well-settled principles of claim construction establish that "the scope of patent protection" will be defined by "[t]he claims, not specification embodiments." Kara Technology Inc. v. Stamps.com Inc., 582 F.3d 1341, 1348 (Fed. Cir. 2009). Thus, a court may not limit the scope of the claims to a "preferred embodiment or import a limitation from the specification into the claims." Id. (citing Phillips, 415 F.3d at 1323). Moreover, a claim generally will not be confined to the embodiments described in the specification "unless the patentee has demonstrated a 'clear intention' to limit

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the claim's scope with 'words or expressions of manifest exclusion or restriction.'" I4I Limited Partnership v. Microsoft Corporation, 598 F.3d 831, 843 (Fed. Cir. 2010) (quoting Liebel-Flarsheim, 358 F.3d at 907-08).

Nothing in the '344 patent establishes that Dey used the embodiment to define the disputed phrase "with reasonable clarity, deliberateness, and precision." In re Paulson, 30 F.3d at 1480. Mindful of the Federal Circuit's repeated warnings against limiting the scope of the claims to specific embodiments, the Court rejects Teva's proposal to limit Dey's claims in this manner. See Kara Technology, 582 F.3d at 1347.

IV. CONCLUSION

For the reasons discussed, the Court **CONSTRUES** the contested claim terms and phrases as follows:

1. "Formulated at a concentration suitable for direct administration" means "ready to administer directly to a subject in need thereof, without mixing or diluting;"
2. "Pharmaceutical composition" means "a medicinal formulation containing an active drug and inert excipients;"
3. "Shelf life" means "the period of time during which a drug may be stored and remains suitable for use;" and

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4. "Formulated for single dosage administration" means "formulated in a quantity that is taken or administered at one time."

Further, the Court adopts the parties' agreed claim constructions and **CONSTRUES** the following terms and phrases as follows:

1. "Stable during long term storage" means "the composition has an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C and greater than or equal to 1, 2 or 3 years storage time at 5° C;"
2. "Article of manufacture" means something that "contains (1) packaging material, (2) a composition, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and (3) a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction;"
3. "Packaging material or pharmaceutical packaging material" means "blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any

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Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd.,
and Teva Pharmaceuticals USA, Inc.*

Case No. 2014-1434

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

DEY, L. P. and DEY, INC.,

Plaintiffs,

v. // CIVIL ACTION NO. 1:09CV87
(Judge Keeley)

TEVA PARENTERAL MEDICINES, INC.,
TEVA PHARMACEUTICALS USA, INC., and
TEVA PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants.

ORDER GRANTING PLAINTIFFS'
MOTION FOR PARTIAL SUMMARY JUDGMENT [DKT. NO. 159]

Pending before the Court is the Motion for Partial Summary Judgment of the plaintiffs, Dey, L.P. and Dey Inc. (collectively "Dey"). (Dkt. No. 159). Dey seeks summary judgment as to whether the proposed production and marketing of a generic version of Perforomist® by the defendants, Teva Parenteral Medicines, Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceuticals Industries, Ltd. (collectively "Teva"), will infringe two claims of one of Dey's family of patents for that drug. For the reasons discussed below, the Court **GRANTS** Dey's motion. (Dkt. No. 159).

I. FACTS AND PROCEDURAL HISTORY

A.

This patent infringement case involves four United States Patents issued to Dey, including 6,667,344 ("the '344 Patent"), 6,814,953 ("the '953 Patent"), 7,348,362 ("the '362 Patent"), and 7,462,645 ("the '645 Patent") (collectively, the "patents-in-suit"). The '344 and '953 Patents, entitled "Bronchodilating

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Compositions and Methods," derive from provisional U.S. patent application 60/284,606 and share essentially identical specifications. The '362 and '645 Patents, entitled "Bronchodilating Beta-Agonist Compositions and Methods," derive from provisional U.S. patent application 60/486,386. They too share essentially identical specifications that closely resemble those of the '344 and '953 Patents.

The patents-in-suit cover aqueous compositions of formoterol that allow the compositions to remain suitable for direct administration during long-term storage. They also cover methods for using these compositions to treat broncho-constrictive disorders. Dey uses the formulations and methods described in these patents in a commercial product known as Perforomist®.

In a letter dated May 12, 2009, Teva, the world's largest manufacturer of generic drugs, notified Dey that it had filed an Abbreviated New Drug Application ("ANDA") seeking United States Food and Drug Administration ("FDA") approval to market a generic version of Perforomist® (Teva's "proposed generic drug product"). Teva also filed a certification with the FDA alleging that the four patents issued to Dey for Perforomist® are invalid, unenforceable, and not infringed by Teva's manufacture or sale of the proposed generic drug product. See 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

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Dey responded to Teva's ANDA by filing this lawsuit under the Hatch-Waxman Act, which "gives a drug patent owner the right to bring an action for infringement upon the filing of a paragraph IV certification." Bristol-Myers Squibb Co. v. Royce Laboratories, Inc., 69 F.3d 1130, 1135 (Fed. Cir. 1995) (citing 35 U.S.C. § 271(e)(2)(A)). Dey alleges that Teva's proposed generic drug product infringes on certain claims in the patents-in-suit, specifically claims 1-14, 16-22, 27-31, 33-39, 48, 61-62, 65, and 69-74 of the '344 Patent, claims 1-13, 15-21, 26-30, 32-38, 58-63, 74-86, 90-94, 99-103, 105-111, and 131-136 of the '953 Patent, claims 1-15 of the '362 Patent, and claims 1-3, and 5-9 of the '645 Patent (collectively, the "asserted claims").

B.

Following briefing and a hearing on the parties' proposed claim constructions, on June 17, 2011, the Court entered an Order that construed the contested claim terms as follows:

1. **"Formulated at a concentration suitable for direct administration"** means "ready to administer directly to a subject in need thereof, without mixing or diluting;"
2. **"Pharmaceutical composition"** means "a medicinal formulation containing an active drug and inert excipients;"

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3. **"Shelf life"** means "the period of time during which a drug may be stored and remains suitable for use;" and

4. **"Formulated for single dosage administration"** means "formulated in a quantity that is taken or administered at one time."

(Dkt. No. 99).

The Court also adopted the parties' agreed constructions of the following terms:

1. **"Stable during long term storage"** means "the composition has an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C and greater than or equal to 1, 2 or 3 years storage time at 5° C;"

2. **"Article of manufacture"** means something that "contains (1) packaging material, (2) a composition, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and (3) a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction;"

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utilizes methods known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or a vibrating orifice;" and

6. **"Without dilution or other modification"** means "a pharmaceutical composition that has not been diluted or changed in any other way."

Id.

C.

On September 21, 2012, Dey filed a motion for partial summary judgment. Based on this Court's claim construction, it asserted that Teva's proposed generic drug product infringes every element of claims 1 and 65 of the '344 Patent. (Dkt. No. 160 at 4). In its response to the motion, Teva contended that, because the formoterol fumarate inhalation solution (the "formoterol solution") in its proposed generic drug product degrades when exposed to sunlight, if not protected by a foil overwrap, its product was not "stable during long-term storage," and consequently did not satisfy the elements of either claim 1 or claim 65, which depends upon claim 1. Teva also contended that its proposed generic drug product does not include the "label" required by claim 65.¹ Dey's reply reiterated

¹ Teva also filed a fifty-six page document entitled "Teva's Response to Plaintiffs' Apparent Statement of Facts and Teva's Rebuttal Statement of Additional Material Facts in Opposition to Dey's Motion for Partial Summary Judgment." (Dkt. No. 163-1). As noted by Dey, this

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that Teva's proposed generic drug product infringes all elements of claims 1 and 65 of the '344 Patent.

II. SUMMARY JUDGMENT STANDARD

"An issue may be decided by summary judgment when no question of material fact is in dispute, or when the nonmovant cannot prevail as a matter of law, even on its view of the facts and evidence." Ateliers de la Haute-Garonne v. Broetje Automation USA Inc., No. 2012-1038, 2013 WL 2181239, at *4 (Fed. Cir. May 21, 2013) (citing Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 587 (1986); Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 251-52 (1986) (citing Fed. R. Civ. P. 56(c)); Allied Colloids, Inc. v. American Cyanamid Co., 64 F.3d 1570, 1573 (Fed. Cir. 1995)). At summary judgment, a court must view all facts in the light most favorable to the nonmoving party and draw all justifiable inferences in its favor. Auto. Techs. Int'l v. BMW of N. Am., Inc., 501 F.3d 1274, 1281 (Fed. Cir. 2007).

Once the moving party identifies those portions of the "the pleadings, the discovery and disclosure materials on file, and any

document does not comply with Local Rule of Civil Procedure 7.02(a) and (b) ("Rule 7.02"), which limits memoranda in response to "twenty-five [double-spaced] pages." See Fed. R. Civ. P. 83 (authorizing district courts to make and amend rules, not inconsistent with the Federal Rules of Civil Procedure, governing practices within the district court). Although Rule 7.02 empowers the Court to enlarge the page limits for good cause shown, Teva made no such motion. Instead, it essentially filed a seventy-five page brief without the leave of the Court.

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affidavits [that] show that there is no genuine issue as to any material fact," Fed. R. Civ. P. 56(c), the burden then shifts to the non-moving party to set forth "some evidence in the record sufficient to suggest that his view of the issue might be adopted by a reasonable factfinder.'" Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 45 F.3d 1550, 1561 (Fed. Cir. 1995) (quoting Resolution Trust Corp. v. Juergens, 965 F.2d 149, 151 (7th Cir. 1992)). The non-moving party, however, cannot rely on contradictions or conflicts within its own evidence. Barwick v. Celotex Corp., 736 F.2d 946, 960 (4th Cir. 1984).

III. LEGAL ANALYSIS

A.

An infringement analysis entails two steps. The first step determines the meaning and scope of the patent claims asserted to be infringed. The second step compares the properly construed claims to the device accused of infringing. Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996) (citations omitted). Here, the Court has already determined the meaning and scope of the disputed claims, and thus must compare Teva's proposed generic drug product to those claims. Importantly, it must compare Teva's proposed generic drug product to the asserted claims of the patents-in-suit rather than

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to Dey's product, Perforomist®. See Zenith Labs., Inc. v. Bristol-Meyers Squibb Co., 19 F.3d 1418, 1423 (Fed. Cir. 1994).

When comparing the accused device to the claims, "the accused device infringes if it incorporates every limitation of a claim, either literally or under the doctrine of equivalents." MicroStrategy Inc. v. Business Objects, S.A., 429 F.3d 1344, 1352 (Fed. Cir. 2005) (citations omitted).² Thus, if "even one claim limitation is missing or not met, there is no literal infringement." Id. Moreover, where a dependant claim is allegedly infringed, the Court cannot find literal infringement unless all of the elements and limitations in both the dependent claim and the independent claim on which it relies have been infringed. See Wahpeton Canvas Co., Inc. v. Frontier, Inc., 870 F.2d 1546, 1553 (Fed. Cir. 1989).

"[W]hile claim construction is a question of law, infringement . . . is a question of fact." Serio-US Ind., Inc. v. Plastic Recovery Tech. Corp., 459 F.3d 1311, 1316 (Fed. Cir. 2006) (citing Optical Disc. Corp. v. Del Mar Avionics, 208 F.3d 1324, 1333-34 (Fed. Cir. 2000); Bai v. L & L Wings, Inc., 160 F.3d 1350, 1353 (Fed. Cir. 1998); Cybor Corp. v. FAS Techs. Inc., 138 F.3d 1448,

² Dey alleges only literal infringement in this motion; thus, it has waived any argument of infringement under the doctrine of equivalents. See Abbott Labs. v. Syntro Research, Inc., 334 F.3d 1343, 1355 (Fed. Cir. 2003).

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1451 (Fed. Cir. 1998) (en banc)). Where "the parties do not dispute any relevant facts regarding the accused product . . . , the question of literal infringement collapses into claim construction and is amenable to summary judgment." Gen. Mills, Inc. v. Hunt-Wesson, Inc., 103 F.3d 978, 983 (Fed. Cir. 1997). "[I]n an action [such as this, brought] under § 271(e)(2)(A) . . . the alleged infringement is not based upon a product that actually exists and can be compared to the claim limitations." Apotex, Inc. v. Cephalon, Inc., 2:06-CV-2768, 2012 WL 1080148, *6 (E.D. Pa. Mar. 28, 2012), aff'd, 500 F. App'x 959 (Fed. Cir. 2013).

Nevertheless, "[b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." Id. (quoting Abbott Laboratories v. TorPharm, Inc., 300 F.3d 1367, 1373 (Fed. Cir. 2002)). Thus, the Court must limit its inquiry "to the ANDA itself, materials submitted by the ANDA applicant in support of the ANDA, and any other relevant evidence submitted by the applicant or patent holder." Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1248-49 (Fed. Cir. 2000).

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Dey, as the patentee, bears the burden of proving infringement by a preponderance of the evidence. Laitram Corp. v. Rexnord, Inc., 939 F.2d 1533, 1535 (Fed. Cir. 1991). "The burden of showing something by a preponderance of the evidence . . . simply requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence." Salem v. Holder, 647 F.3d 111, 116 (4th Cir. 2011) (citing United States v. Manigan, 592 F.3d 621, 631 (4th Cir. 2010)). At bottom, "[s]ummary judgment on the issue of infringement [or noninfringement] is proper when no reasonable jury could find that every limitation recited in a properly construed claim either is or is not found in the accused device either literally or under the doctrine of equivalents." PC Connector Solutions, LLC v. SmartDisk Corp., 406 F.3d 1359, 1364 (Fed. Cir. 2005) (citing Bai, 160 F.3d at 1353-54).

B.

Dey argues there is no genuine dispute of material fact that Teva's proposed generic drug product infringes claims 1 and 65 of the '344 Patent, and that it is entitled to judgment as a matter of law as to these claims. Dey bears the burden of proving infringement by a preponderance at trial. The Court therefore will first review claims 1 and 65, and then consider Dey's evidence that

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1. Pharmaceutical Composition

Limitation	Portion of the record cited by Dey in support of partial summary judgment
A pharmaceutical composition	<p>Table 2.3.P.1-1 (dkt. no 160-9 at 1)</p> <ul style="list-style-type: none"> Active ingredient, formoterol fumarte dihydrate Various inactive ingredients <p>Teva's proposed product label (dkt. no. 160-11 at 23)</p> <ul style="list-style-type: none"> "Each vial contains 2 mL of a clear colorless solution composed of formoterol fumarate dihydrate"

The first phrase of claim 1 recites: "A pharmaceutical composition" In its Markman order, the Court construed that phrase to mean "a medicinal formulation containing an active drug and inert excipients." (Dkt. No. 99 at 41). Based upon Table 2.3.P.1-1: Unit Composition for Formoterol Fumurate Inhalation Solution ("Table 2.3.P.1-1") (dkt. no. 160-9 at 1), excerpted from Teva's ANDA, and Teva's proposed label for its proposed generic drug product (dkt. no. 160-11 at 23), Dey argues that Teva's proposed generic drug product contains a "pharmaceutical composition comprising formoterol," and, thus, the limitation is found in Teva's proposed generic drug product.

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Table 2.3.P.1-1, in relevant part, states that the active component in Teva's proposed generic drug product is "Formoterol Fumarate Dihydrate, USP," and that the formoterol solution also contains Citric Acid, USP (buffering agent), Sodium Citrate, USP (buffering agent), Sodium Chloride, USP (tonicity agent), and Water for Injection, USP (vehicle). (Dkt. No. 160-9 at 1). Teva's proposed label for the proposed generic drug product also states that

[f]ormoterol fumarate inhalation solution is supplied as 2 mL of formoterol fumarate inhalation solution packaged in a 3 mL single-use low-density polyethelene vial and overwrapped in a foil pouch. Each vial contains 2 mL of a clear, colorless solution composed of formoterol fumarate dihydrate equivalent to 20 mcg of formoterol fumarate in an isotonic, sterile aqueous solution containing sodium chloride, pH adjusted to 5.0 with citric acid and sodium citrate.

(Dkt. No. 160-11 at 23).

Importantly, "Teva does not contest that [its] formoterol fumarate solution is a medicinal formulation containing formoterol fumarate dihydrate as the active pharmaceutical ingredient and inert excipients such as water and sodium chloride." (Dkt. No. 163-1 at 19). Nor does "Teva[] contest [that] the table is from Teva's ANDA and sets forth the general composition of Teva's generic formoterol fumarate inhalation solution and the corresponding pharmaceutical function and amount per unit basis of each component." Id.

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Consequently, the evidence preponderates in favor of the conclusion that Teva's proposed generic drug product contains a medicinal formulation composed of an active drug (Formoterol Fumarate Dihydrate, USP) and several excipients, or inactive substances, including citric acid, sodium citrate, sodium chloride, and water. Thus, when compared to the Court's construction of the limitation, "pharmaceutical composition," the first limitation of claim 1 plainly is found in Teva's proposed generic drug product.

2. Comprising Formoterol, or a Derivative Thereof

Limitation	Portion of the record cited by Dey in support of partial summary judgment
Comprising formoterol, or a derivative thereof	<p>Table 2.3.P.1-1 (dkt. no. 160-9 at 1)</p> <ul style="list-style-type: none"> • Active ingredient, formoterol fumarate dihydrate <p>Teva's proposed product label (dkt. no. 160-11 at 23)</p> <ul style="list-style-type: none"> • "Each vial contains 2 mL of a clear colorless solution composed of formoterol fumarate dihydrate"

Claim 1 next recites that the pharmaceutical composition is comprised of "formoterol, or a derivative thereof." Once again, Dey relies on Table 2.3.P.1-1 (dkt. no. 160-9 at 1), and Teva's proposed product label (dkt. no. 160-11 at 23), as evidence that Teva's proposed generic drug product is a pharmaceutical composition "comprising formoterol, or a derivative thereof."

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Dey's evidence supports the conclusion that Teva's proposed generic drug product contains this limitation. Specifically, Table 2.3.P.1-1 states that "Formoterol Fumuarate Dihydrate, USP" is the active ingredient of Teva's proposed generic drug product (dkt. no. 160-9 at 1), and Teva's proposed label for the proposed generic drug product names "formoterol fumarate dihydrate" as the proposed generic drug product's active ingredient. (Dkt. No. 160-11 at 23). Recall that "Teva does not contest that [its] formoterol fumarate solution is a medicinal formulation containing formoterol fumarate dihydrate as the active pharmaceutical ingredient and inert excipients such as water and sodium chloride," (dkt. no. 163-1 at 19), or that Table 2.3.P.1-1 "sets forth the general composition of Teva's generic formoterol fumarate inhalation solution and the corresponding pharmaceutical function and amount per unit basis of each component." Id. In short, Dey has met its initial burden on summary judgment of establishing the presence of this limitation in Teva's proposed generic drug product.

3. In a Pharmacologically Suitable Aqueous Solution

Limitation	Portion of the record cited by Dey in support of partial summary judgment
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In a pharmacologically suitable aqueous solution	Table 2.3.P.1-1 (dkt. no. 160-9 at 1) <ul style="list-style-type: none">• Vehicle, water for injection Teva's proposed product label (dkt. no. 160-11 at 23) <ul style="list-style-type: none">• "isotonic, sterile aqueous solution"
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Next, Dey argues that the pharmaceutical composition found in Teva's proposed generic drug product is "formulated as a pharmacologically suitable aqueous³ solution," thus satisfying the third limitation found in claim 1. Again, Dey draws upon Table 2.3.P.1-1 (dkt. no. 160-9 at 1) and Teva's proposed product label for the proposed generic drug product. (Dkt. No. 160-11 at 23).

Table 2.3.P.1-1 states that Teva's proposed generic drug product contains "water for injection." (Dkt. No. 160-9 at 1), and Teva's proposed product label states that "[e]ach vial contains 2 mL of clear, colorless solution composed of formoterol fumarate dihydrate . . . in an isotonic, sterile aqueous solution." (Dkt. No. 160-11 at 23). Moreover, Teva does not contest that its "formoterol fumarate solution is a medicinal formulation containing formoterol fumarate dihydrate as the active pharmaceutical ingredient and inert excipients such as water and sodium chloride." (Dkt. No. 163-1 at 19). It follows from this evidence that it is

³ Merriam-Webster's Third International Dictionary, Unabridged 2002 (Merriam-Webster, Inc., 3d ed. 2002) ("Webster's") second definition of "aqueous" - the one relevant here - is "made from, with, or by means of water." Webster's 108 (2002).

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more likely than not that Teva's proposed generic product is formulated as a pharmacologically suitable aqueous solution. Dey thus has met its initial burden on summary judgment as to this limitation.

4. Wherein the Composition is Stable During Long Term Storage

Limitation	Portion of the record cited by Dey in support of partial summary judgment
Wherein the composition is stable during long term storage	Teva's long-term stability studies (dkt. no. 160-12 at 1) Teva's Development Stability Report (dkt. no. 160-14 at 12) • "All the specification limits were met for product"

The Court's Markman order already construed the phrase "stable during long term storage" to mean that "the composition has an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C and greater than or equal to 1, 2 or 3 years storage time at 5° C." It also construed the phrase "shelf life" to mean "the period of time during which a drug may be stored and remains suitable for use." (Dkt. No. 99 at 41).

Dey points to two items in the record to support its contention that this limitation is found in Teva's proposed generic

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Limitation	Portion of the record cited by Dey in support of partial summary judgment
The composition is formulated at a concentration effective for bronchodilation	Teva's proposed label (dkt. no. 160-11 at 24, 36, 14)

Claim 1 next recites that the "composition [i.e., the pharmaceutical composition] is formulated at a concentration effective for bronchodilation." To demonstrate that Teva's proposed generic drug product contains this limitation, Dey again points to portions of Teva's proposed label, which states:

- "Inhaled formoterol fumarate acts locally in the lungs as a bronchodilator" (dkt. no. 160-11 at 24);
- "Formoterol fumarate inhalation solution is a medicine called a long-acting beta₂-agonist (LABA) or long-acting bronchodilator" id. at 36);
- Formoterol fumarate inhalation solution is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction" Id. at 14.

These statements indicate that Teva intends its proposed generic product to act as a bronchodilator. Indeed, Teva is statutorily bound to do so. See Apotex, Inc., 2012 WL 1080148, at *6. Moreover, "Teva does not dispute that its formoterol fumarate

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inhalation solution is formulated at a concentration of formoterol fumarate such that when administered to a patient via nebulization, the nebulized solution is effective for bronchodilation in certain COPD patients." (Dkt. No. 163-1 at 21). Accordingly, Dey has met its initial burden on summary judgment of adducing evidence that preponderates in favor of the conclusion that Teva's proposed generic product is formulated at a concentration effective for bronchodilation.

6. Nebulization

Limitation	Portion of the record cited by Dey in support of partial summary judgment
By nebulization	Teva's proposed label (dkt. no. 160-11 at 10, 14, 35, 40)

The pharmaceutical composition described in claim 1 also must be "formulated at a concentration effect[ive] for bronchodilation by nebulization." Once again, Dey relies on portions of Teva's proposed label to support its contention that this claim is found in Teva's proposed generic drug product. Dey points to Teva's proposed label, which states as follows:

- "For use with a standard jet nebulizer (with a facemask or mouthpiece) connected to an air compressor (2)" (dkt. no. 160-11 at 10);

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- "The recommended dose of formoterol fumarate inhalation solution is one 20 meg unit-dose administered twice daily (morning and evening) by nebulization" id. at 14;
- "It is important that patients understand how to use formoterol fumuarate inhalation solution with a nebulizer" id. at 35; and
- "Formoterol fumarate inhalation solution is used only in a standard jet nebulizer machine connected to an air compressor." Id. at 40.

Moreover, "Teva does not dispute that its formoterol fumarate solution is formulated at a concentration of formoterol fumurate such that when administered to a patient via nebulization, the nebulized solution is effective for bronchodilation in certain COPD patients." (Dkt. No. 163-1 at 21). Considering the statements on Teva's proposed label and Teva's telling admission, the Court concludes that Teva's proposed generic product includes the limitation "by nebulization." Dey therefore has met its initial burden on summary judgment as to this particular limitation.

7. Suitable for Direct Administration To a Subject in Need Thereof, Without Propellant and Without Dilution of the Composition Prior to Administration

Limitation	Portion of the record cited by Dey in support of partial summary judgment
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Suitable for direct administration to a subject in need thereof, without propellant and without dilution of the composition prior to administration	Teva's proposed label (dkt. no. 160-11 at 38, 41-42, 63) Table 2.3.P.1-1 (dkt. no 160-9 at 1)
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Dey argues that Teva's proposed generic product satisfies this limitation of claim 1. Importantly, the Court has construed the phrase "formulated at a concentration suitable for direct administration," which is a component of this limitation, to mean "ready to administer directly to a subject in need thereof, without mixing or diluting." (Dkt. No. 99 at 7, 41).

Teva's proposed label states that the "formoterol fumarate inhalation solution [is to be used] exactly as prescribed. One ready-to-use vial of formoterol fumarate inhalation solution is one dose." (Dkt. No. 160-11 at 38); see also (Dkt. No. 160-11 at 63 (same)). It also states that Teva's proposed generic drug product "does not require dilution prior to administration by nebulization." Id. at 24. The detailed instructions included in the proposed generic drug product label do not direct users to mix the pharmaceutical composition with any other substance before administering it. See id. at 41-42. Nor does Teva's proposed generic drug product contain any ingredient described as a "propellant." See (Dkt. No. 160-9 at 1) (listing ingredients of

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Teva's proposed generic drug product, which include active components, buffering agents, tonicity agents, and a vehicle). These omissions, and Teva's characterization of its proposed generic drug product as "ready to use," support the conclusion that Teva's proposed generic product satisfies the limitation of claim 1, "suitable for direct administration without propellant and without dilution of the composition prior to administration."

The Court turns next to the limitations contained in claim 65 of the '344 Patent.

8. Article of Manufacture

Limitation	Portion of the record cited by Dey in support of partial summary judgment
<p>Article of manufacture is something that contains:</p> <ul style="list-style-type: none"> • packaging material; • a composition, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction; and • a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction. 	<p>Teva's proposed label (dkt. no. 160-11 at 1, 5, 7, and 14)</p>

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The Court has construed "article of manufacture" (dkt. no. 99) to mean something that "contains (1) packaging material, (2) a composition, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and (3) a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction." Dey argues that Teva's proposed generic drug product meets these three elements of an "article of manufacture" because (1) Teva's proposed generic product is sold in packaging material; (2) the product is indicated for the treatment of chronic obstructive pulmonary disease ("COPD"); and (3) the product includes a label that instructs users how to administer the drug.

Dey's contention that Teva's proposed label indicates its proposed generic drug product contains packaging material is correct. For the purposes of the patents-in-suit, "packing material" means "blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment." (Dkt. No. 99 at 42-43). Teva's proposed label indicates that its proposed generic drug product

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contains a carton (dkt. no. 160-11 at 1), a five-pack nebule, id. at 5, and a foil pack, id. at 7, all of which plainly satisfy this Court's construction of the term "packaging material."

Moreover, Teva's proposed label states that "[f]ormoterol fumarate inhalation solution is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction" Id. at 14. That statement establishes both that Teva's proposed generic drug product is useful for the treatment of bronchoconstriction, and also that the label indicates such utility. Dey therefore has met its initial burden on summary judgment as to the limitation "article of manufacture."⁴

2. Formulated for Single Dosage Administration

Dey argues that Teva's proposed generic drug product is "formulated for single dosage administration," and thus contains the final limitation of claim 65. The Court's Markman order construed that phrase to mean "formulated in a quantity that is taken or administered at one time." (Dkt. No. 99 at 42).

⁴ Teva objects that its proposed generic drug product is not an article of manufacture because it does not include a label that states, "the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction" (Dkt. No. 163-1 at 23). The Court will address this argument, which is also raised in Teva's response brief (dkt. no. 163 at 20 - 22), infra.

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Additionally, the Court noted that the ordinary meaning of the term "formulate" is "create." (Dkt. No. 99 at 16).

Teva's proposed label for its generic drug product states that the "formoterol fumarate inhalation solution [is to be used] exactly as prescribed. One ready-to-use vial of formoterol fumarate inhalation solution is one dose." (Dkt. No. 160-11 at 38); see also (Dkt. No. 160-11 at 63 (same)). Given the ordinary meaning of "formulated" noted in the Court's Markman order, Teva's proposed label plainly indicates that the formoterol solution, which is a part of its proposed generic drug product, is to be "created" (dkt. no. 99 at 16) for use in a "ready-to-use vial" which, in turn, is one dose of the proposed generic drug product. (Dkt. No. 160-11 at 38); see also (Dkt. No. 160-11 at 63 (same)). When compared to the language of claim 65 - that the described "article of manufacture" is comprised, in part, by "an aqueous composition comprising the composition of claim 1 formulated for single dosage administration" - Teva's statement supports Dey's contention that this limitation is, more likely than not, present in Teva's proposed generic drug product. Dey, therefore, has met its initial burden on summary judgment as to this limitation.

Teva's response, that "[a] drug product is not 'formulated' for single dose administration," is inapposite. "Drug product" is Dey's phrase. See (Dkt. No. 160 at 9). It is not found in claim 65

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of the '344 Patent. Rather, claim 65 requires the "aqueous composition comprising the composition of claim 1" to be formulated for "single dose administration." MicroStrategy Inc., 429 F.3d at 1352 ("the accused device infringes if it incorporates every limitation of a claim, either literally or under the doctrine of equivalents").

In sum, the Court concludes that Dey has identified portions of Teva's proposed label and other discovery materials that "show that there is no genuine issue as to any material fact." Fed. R. Civ. P. 56(c). With regard to claim 1, Dey has identified portions of the record that support its contention that each limitation of claim 1 is contained in Teva's proposed generic drug product. Likewise, Dey has also identified portions of the record that support its contention that Teva's proposed generic drug product contains every limitation of claim 65.

Based on these conclusions, the burden now shifts to Teva, the non-moving party, to set forth "some evidence in the record sufficient to suggest that [its] view of the issue might be adopted by a reasonable factfinder.'" Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 45 F.3d 1550, 1561 (Fed. Cir. 1995) (quoting Resolution Trust Corp. v. Juergens, 965 F.2d 149, 151 (7th Cir. 1992)). Absent such a showing by Teva, Dey is entitled to partial summary judgment on its contention that, as a

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matter of law, Teva has infringed claims 1 and 65 of the '344 Patent.

D.

Teva's response to Dey's motion for partial summary judgment focuses on what it characterizes as material factual disputes as to two limitations - the first in claim 1, and the second in claim 65. First, Teva argues that its proposed generic drug product does not contain the limitation of long-term stability found in claim 1 because, absent a light-protective foil overwrap, the formoterol solution degrades when exposed to light. Teva argues that the formoterol solution therefore is not "stable during long term storage." (Dkt. No. 163 at 4).

Teva also argues that its proposed generic drug product does not contain the label required by claim 65 because the label in its proposed generic product is not found on the vial containing the formoterol solution. *Id.* at 15. Alternatively, it contends that its label does not satisfy claim 65 because it does not include any matter stating that the formoterol solution "is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled

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stable during long term storage. Based on its conception of claim 1, Teva concludes that, because "composition" refers to the preceding phrase, "pharmaceutical composition," claim 1 plainly requires the pharmaceutical composition **itself** to be stable during long term storage. Therefore, according to Teva, because the formoterol solution - absent any protective overwrap - included in its proposed generic drug product degrades when exposed to sunlight, the formoterol solution, i.e., pharmaceutical composition, is not "stable during long term storage," does not satisfy claim 1, and therefore does not infringe the '344 Patent.

Teva's argument fails for the fundamental reason that claim 1 of the '344 Patent simply does not address photostability. See (Dkt. No. 165-3 at 3-4). One cannot find it in the body of the '344 Patent. (Dkt. No. 163-18 at 8). It is not referenced in the construction of the limitation "stable during long term storage." (Dkt. No. 99 at 42) ("'Stable during long term storage' means 'the composition has an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C and greater than or equal to 1, 2 or 3 years storage time at 5° C.'"). Nor is any reference to photostability found in the undisputed definition of "stable" contained in the '344 and '953 patents.

As used herein, the stability of a composition provided herein refers to the length of time at a given temperature that is greater than 80%, 85%, 90% or 95% of

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the initial amount of active ingredient, e.g., formoterol, is present in the composition. Thus, for example, a composition that is stable for 30 days at 25° C. would have greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient present in the composition at 30 days following storage at 25° C.

'344, col. 5, ll. 30-38; '953, col. 5, ll. 40-48.

That definition includes two independent variables, time and temperature, and one dependent variable, the percentage of the initial amount of active ingredient present in the composition following a period of storage. See id. Contrary to Teva's rebuttal argument, the independent variable of exposure to light and/or ultraviolet ("UV") radiation simply is not part of that definition. In other words, the degradation of the amount of active ingredient present in the composition due to light exposure - within or without a light-protective foil overwrap - is not a variable that is relevant to the determination of long term stability under the undisputed definition of "stability" found in the '344 Patent, or the Court's construction of the limitation "stable during long storage." See (Dkt. No. 163 at 9).⁶

⁶ This conclusion carries two implications. First, photostability also is not a limitation implicit in claim 65 of the '344 Patent, because that claim depends upon claim 1. Second, because the Court has concluded that photostability is irrelevant to the issue of long term stability, it need not address Teva's argument that its formoterol solution itself, absent packaging, must remain stable during long term storage.

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It appears that Teva has relocated its "intrinsic stability" argument from the context of the limitation, "pharmaceutical composition," where Teva placed it during the Markman briefing, to the subsequent limitation, "stable during long term storage." That conclusion is obvious when one considers that the bottom line of Teva's argument on summary judgment is that, in order to be considered stable during long term storage, the percentage of the initial amount of active ingredient present in the pharmaceutical composition described in claim 1, absent any sort of packaging, cannot decrease when exposed to light. Stated differently, Teva argues that the pharmaceutical composition described in claim 1 possesses the essential quality of photostability, i.e., the pharmaceutical composition is intrinsically stable.

At bottom, "Dey never asserted that its pharmaceutical compositions had an inherent characteristic of 'stability' distinct from being 'stable during long term storage,'" (dkt. no. 99 at 27), a limitation defined by the variables of the time and temperature. Thus, for the same reason that it rejected Teva's argument in its Markman opinion, the Court rejects the argument again on summary judgment. See id. at 19-27. Therefore, Teva's objection that its proposed generic drug product is not stable during long term storage, absent a foil overwrap, because the formoterol solution

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included in that product degrades when exposed to light, fails as a matter of law.

2.

Next, Teva argues that its proposed generic drug does not contain a "label," as required by claim 65 of the '344 Patent, because the label contained in its proposed generic product is not found "upon" the vial containing the formoterol solution. Id. at 15. In support of its argument, Teva relies on the construction of that limitation adopted by the Southern District of New York in Dey, Inc. v. Sepracor, Inc., No. 07 CIV. 2353 JGK, 2012 WL 1720614 (S.D.N.Y. May 16, 2012) (the "New York litigation"), a parallel proceeding in which claim 65 of the '344 Patent also was in dispute.

Dey first argues that the construction of "label" adopted in the New York litigation has no preclusive effect here as that construction was issued subsequent to the construction by this Court. Second, Dey contends that, because the New York litigation ended not on summary judgment or following a trial, but with a settlement between the parties, the claim construction in that case is not binding in this proceeding. Finally, Dey asserts that it will suffer undue prejudice should the Court adopt the construction from the New York litigation at this late date because, in the year

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following the claim construction ruling in that case, Teva never sought to raise the issue here.

In order to adequately address Teva's response, the Court will first review the proceedings in this case and those in the New York litigation. It will then address the doctrine of res judicata, and more specifically, issue preclusion.

(a)

In March, 2007, Dey filed suit against Sunovion Pharmaceuticals, Inc. ("Sunovion")⁷ in the Southern District of New York, alleging that Sunovion's product, Brovana®, infringed the '344, '953, '362, and '645 patents.⁸ Dey, Inc. v. Sepracor, Inc., 847 F. Supp. 2d 541, 547 (S.D.N.Y. 2012) rev'd and remanded sub nom. Dey, L.P. v. Sunovion Pharmaceuticals, Inc., 715 F.3d 1351 (Fed. Cir. 2013). Thereafter, on June 23, 2009, Dey filed a complaint in this Court alleging that Teva's proposed generic drug product infringed those same patents. See (Dkt. No. 1).

On June 17, 2011, this Court's Markman order construed certain claims at issue in the patents-in-suit, including "label," a limitation found in claim 65 of the '344 Patent. Significantly,

⁷ At the time of filing, Sunovion Pharmaceuticals, Inc. ("Sunovion") was known as Sepracor, Inc. ("Sepracor").

⁸ Dey also alleged that Sunovion's product infringed United States Patent Numbers 7,465,756; 7,473,710; and 7,541,385. Dey, Inc., 847 F. Supp. 2d at 547.

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"label" was not among the terms disputed by the parties. Accordingly, the Court adopted the parties' proposed construction that "'label' means 'Printed matter included with the article of manufacture that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.'" (Dkt. No. 99 at 43).

Nearly a year later, on May 16, 2012, the district court in the New York litigation construed the term "label," found in claim 65 of the '344 Patent. Dey, Inc., 2012 WL 1720614, at *10-11. Unlike the instant proceeding, however, Dey and Sunovian contested the construction of "label." Id. The Markman order in the New York litigation adopted Sunovian's proposed construction, and construed "label" to mean "[a] display of written, printed, or graphic matter upon the immediate container surrounding the pharmaceutical product that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction." Id. Eight days after entry of that Markman order, on May 24, 2012, the district court entered a Final Judgment and Order in the New York litigation. (Dkt. No. 163-18 at 120-124).

(b)

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Because the application of issue preclusion is not a matter within the exclusive jurisdiction of the Federal Circuit, the Court will apply the relevant law of the Fourth Circuit. See Vardon Golf Co. v. Karsten Mfg. Corp., 294 F.3d 1330, 1333 (Fed. Cir. 2002). Issue preclusion, a subset of res judicata, "forecloses the relitigation of issues of fact or law that are identical to issues which have been actually determined and necessarily decided in prior litigation in which the party against whom [collateral estoppel] is asserted had a full and fair opportunity to litigate." In re Microsoft Corp. Antitrust Litig., 355 F.3d 322, 326 (4th Cir. 2004) (quoting Sedlack v. Braswell Servs. Group, Inc., 134 F.3d 219, 224 (4th Cir. 1998) (internal quotation marks and citation omitted)).⁹

⁹ The Federal Circuit recently issued an opinion in which it set out that circuit's law as to issue preclusion. See Levi Strauss & Co. v. Abercrombie & Fitch Trading Co., No. 2012-1495, 2013 WL 2991065, at *3-4, --- F.3d --- (Fed. Cir. June 18, 2013). That case, however, was an appeal from The United States Patent and Trademark Office, Trademark Trial and Appeal Board, not an appeal from a district court. In other words, Vardon still requires the Court to apply the issue preclusion rule of the Fourth Circuit. See Senyszyn v. Dep't of Treasury, 465 F. App'x 935, 941 (Fed. Cir. 2012).

Regardless, the tests of the Fourth and Federal Circuit are relatively similar. Compare In re Microsoft Corp. Antitrust Litig., 355 F.3d at 326, with Levi Strauss & Co., 2013 WL 2991065, at *3-4 ("We have stated four preconditions for a second suit to be barred by issue preclusion: (1) identity of the issues in a prior proceeding; (2) the issues were actually litigated; (3) the determination of the issues was necessary to the resulting judgment; and (4) the party defending against preclusion had a full and fair opportunity to litigate the issues.").

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To preclude an issue from relitigation, the proponent of preclusion must demonstrate that

- (1) the issue or fact is identical to the one previously litigated;
- (2) the issue or fact was actually resolved in the prior proceeding;
- (3) the issue or fact was critical and necessary to the judgment in the prior proceeding;
- (4) the judgment in the prior proceeding is final and valid; and
- (5) the party to be foreclosed by the prior resolution of the issue or fact had a full and fair opportunity to litigate the issue or fact in the prior proceeding.

Id. "The burden is on the party asserting collateral estoppel to establish its predicates, and this of course includes presenting an adequate record for the purpose." Allen v. Zurich Ins. Co., 667 F.2d 1162, 1166 (4th Cir. 1982).

Here, Teva, the proponent of issue preclusion, cannot meet its burden under Allen. Nearly one year before entry of the Markman order in the New York litigation, this Court adopted the construction of "label" jointly proposed by Dey and Teva. Even assuming, for argument's sake, that the Markman order in the New York litigation was a final order, it still was not "**previously litigated**," "**resolved in the prior proceeding**," "**critical and necessary to the judgment in the prior proceeding**," a "**judgment in the prior proceeding**," or "**a prior resolution of the issue**." In re

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Microsoft Corp. Antitrust Litig., 355 F.3d at 326 (emphasis added). On that fact alone, it cannot preclude this Court from applying its own construction of "label".

Moreover, even if the district court in the New York litigation had construed "label" prior to this Court's construction of that same term, its Markman order is not a final order having preclusive effect. See, e.g. Powervip, Inc. v. Static Control Components, Inc., 1:08-CV-382, 2011 WL 2669059, at *6 (W.D. Mich. July 6, 2011) ("Given that in construing patent claims judges often must tread on alien ground, addressing scientific and technological concepts that even experts in the field may disagree on, and that district court judges' interpretations are overturned nearly half of the time, the Court questions the utility of applying issue preclusion to a Markman order."); DE Technologies, Inc. v. IShopUSA, Inc., 826 F. Supp. 2d 937, 941 (W.D. Va. 2011) ("the court declines to apply the doctrine of collateral estoppel to the court's prior Markman rulings"); Kollmorgen Corp. v. Yaskawa Electric Corp., 147 F.Supp.2d 464, 467 (W.D.Va. 2001). But see, e.g., TM Patents, L.P. v. International Business Machines Corp., 72 F.Supp.2d 370 (S.D.N.Y. 1999) (giving collateral estoppel effect to a Markman order).

Nor can Teva rely on the Final Order and Judgment entered in the New York litigation to imbue the Markman order in that case

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with the preclusive effect it otherwise lacks. (Dkt. No. 163-18 at 120-124). The Final Order and Judgement is a consent decree, which has "elements of both judgment and contract, a dual character that results in different treatment for different purposes." Smyth ex rel. Smyth v. Rivero, 282 F.3d 268, 280 (4th Cir. 2002) (internal quotations omitted). "In most circumstances, it is recognized that consent agreements ordinarily are intended to preclude any further litigation on the claim presented but are not intended to preclude further litigation on any of the issues presented. Thus consent judgments ordinarily support claim preclusion but not issue preclusion." Arizona v. California, 530 U.S. 392, 414 (2000) (quoting 18 Charles Alan Wright, Arthur R. Miller, & Edward H. Cooper, Federal Practice and Procedure § 4443, pp. 384-385 (1981)).

The Federal Circuit addressed the preclusive effect of consent decrees upon subsequent litigation in Foster v. Hallco Mfg. Co., Inc., 947 F.2d 469, 480 (Fed. Cir. 1991):

A rationale for the rule of issue preclusion is that once a legal or factual issue has been settled by the court after a trial in which it was fully and fairly litigated that **issue** should enjoy repose. Such litigated issues may not be relitigated even in an action on a different claim between the parties. Where a judgment between parties is entered by consent prior to trial on any issue, no issue may be said to have been fully, fairly or actually litigated. Thus, the general rule that issue preclusion does not arise from a consent judgment would allow Foster's challenge to validity on a different claim inasmuch as no issue was actually tried and disposed of by decision of the court in Foster I.

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Foster, 947 F.2d at 480 (internal citations and quotations omitted) (emphasis in original). Nonetheless, "if a consent judgment, by its terms, indicates that the parties thereto intend to preclude any challenge to the validity of a particular patent, even in subsequent litigation involving a new cause of action, then that issue can be precluded. Id. at 480-81.

Here, the Final Order and Judgment in the New York litigation says nothing about the parties' intent to preclude any subsequent litigation as to claim 65 of the '344 Patent. (Dkt. No. 163-18 at 120-124). In fact, as Teva candidly acknowledges, it is silent as to claim 65. Absent an indication that the parties to that consent judgment intended to preclude any further interpretation of claim 65, this Court is left to apply the general rule that issue preclusion does not arise from a consent judgment, and accordingly, concludes that the Final Order and Judgment entered in the New York litigation does not preclude litigation as to claim 65 of the '344 Patent, using this Court's construction of that term.

3.

Finally, Teva argues that its proposed label does not contain the indication required by this Court's construction of that term. Specifically, Teva argues that its proposed label does not include the indication that its product is suited for the treatment of

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asthma, which, according to Teva, the '344 Patent requires. See (Dkt. No. 163 at 20).

To address this argument, the Court turns first to claim 65 and the specifications contained in the '344 Patent.

Claim 65 states:

An article of manufacture, comprising packaging material, an aqueous composition comprising the composition of claim 1 formulated for single dosage administration, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and **a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.**

(emphasis added). Helpfully, the '344 Patent does not leave "undesired and/or uncontrolled bronchoconstriction" undefined. See '344 Patent Col. 6, ll. 57-65. The specification defines the phrase as referring to "bronchoconstriction that results in or from a pathological symptom or condition. Pathological conditions include, but are not limited to, asthma and chronic obstructive pulmonary disease (COPD). Likewise, pathological symptoms include, but are not limited to, asthma and COPD." '344 Patent Col. 6, ll. 57-65.

After reviewing claim 65 and the relevant specification, the Court concludes that Teva's argument lacks merit. "Label," as construed by this Court and without objection from Teva during the

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claims construction process, merely requires that the printed matter included with the article of manufacture "indicate[] that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction." (Dkt. No. 99 at 43). The specification that defines "undesired and/or uncontrolled bronchoconstriction" provides that bronchoconstriction either results:

(1) in a pathological symptom, e.g., asthma or COPD; or

(2) from a pathological condition, e.g., asthma or COPD.

The specification further provides that relevant pathological symptoms and conditions are not limited to asthma or COPD. Similarly, printed matter which Teva proposes to include with its proposed generic product states that "[f]ormoterol fumarate inhalation solution is indicated . . . in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD)." (Dkt. No. 160-11 at 14); see also id. at 37.

Printed matter included with
 Teva's proposed ANDA product

Specification of claim 65 of the
 '344 Patent defining "undesired
 and/or uncontrolled
 bronchoconstriction"

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"Formoterol fumarate inhalation solution is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with **chronic obstructive pulmonary disease (COPD)**, including bronchitis and emphysema." (Dkt. No. 160-11 at 14); see also id. at 37.

"[B]ronchoconstriction that results in or from a pathological symptom or condition. Pathological conditions include, but are not limited to, asthma and **chronic obstructive pulmonary disease (COPD)**. Pathological symptoms include, but are not limited to, asthma and **COPD**."

In other words, Teva's label states that its proposed generic drug product is indicated for the maintenance treatment of bronchoconstriction in patients with COPD. That clearly satisfies the indication required by this Court's construction of the term "label." Teva's argument, that the '344 Patent requires an indication for the treatment of asthma, is not persuasive given the patent's specification that "undesired and/or uncontrolled bronchoconstriction" results "in or from a pathological symptom or condition," which include, but are not limited to, COPD and asthma. Teva therefore has failed to raise a genuine issue of material of fact that would preclude granting partial summary judgment of infringement to Dey.

IV. Conclusion

Dey has met its burden on summary judgment of showing that Teva's proposed generic drug product "[literally] incorporates every limitation of" claims 1 and 65 of the '344 Patent. MicroStrategy Inc., 429 F.3d at 1352, while Teva has failed to meet

DEY, ET AL. V. TEVA, ET AL.

1:09CV87

ORDER GRANTING PLAINTIFFS' MOTION FOR
PARTIAL SUMMARY JUDGMENT

its rebuttal burden to set forth “‘some evidence in the record sufficient to suggest that [its] view of the issue might be adopted by a reasonable factfinder.’” Glaverbel Societe Anonyme, 45 F.3d at 1561. Accordingly, the Court **GRANTS** Dey’s Motion for Partial Summary Judgment of Infringement. (Dkt. No. 159). This case remains on the Court’s trial docket and is scheduled as the first case on Monday, July 29, 2013.

It is so ORDERED.

The Court directs the Clerk of Court to transmit copies of this Order to counsel of record.

DATED: July 17, 2013.

/s/ Irene M. Keeley
IRENE M. KEELEY
UNITED STATES DISTRICT JUDGE

*Dey L.P., Now Known as Mylan Specialty, L.P., and Dey, Inc. v.
Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd.,
and Teva Pharmaceuticals USA, Inc.*

Case No. 2014-1434

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
AT CLARKSBURG

FILED
JUL 29 2013
U.S. DISTRICT COURT
CLARKSBURG, WV 26301

DEY, L.P. and DEY, INC.,

Plaintiffs,

v.

TEVA PARENTERAL MEDICINES, INC.,
TEVA PHARMACEUTICALS USA, INC., and
TEVA PHARMACEUTICAL INDUSTRIES,
LTD.,

Defendants.

Civil Action No. 1:09-cv-87
(Judge Keeley)

PROPOSED STIPULATION AND ORDER

WHEREAS, Plaintiffs allege that Defendants infringe the following claims of the following patents: Claims 2, 3, 34, 40, 62, 65, 74, 90, 104, and 116 of U.S. Patent No. 6,667,344 (the "'344 Patent"); Claims 75, 76, 106, 112, 136, 154, 160, and 163 of U.S. Patent No. 6,814,953 (the "'953 Patent"); Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 of U.S. Patent No. 7,348,362 (the "'362 Patent"); and Claims 1, 2, 3, 5, 6, 7, 8, and 9 of U.S. Patent No. 7,462,645 (the "'645 Patent") (collectively, the "Asserted Claims");

WHEREAS, in an Order dated July 17, 2013 (the "Summary Judgment Order"), the Court entered partial summary judgment finding that Defendants infringe Claims 1 and 65 of the '344 Patent, as construed in the Court's Memorandum Opinion and Order dated June 17, 2011 (the "Markman Order"); and

WHEREAS the parties wish to streamline the trial in this matter without prejudice to their rights to appeal the Court's Markman Order, Summary Judgment Order, and the reasoning contained therein;

IT IS HEREBY STIPULATED AND AGREED by the parties hereto, subject to the approval of the Court and the reservation of rights herein, that:

1. For the purpose of this civil action, Defendants stipulate that their ANDA Products in ANDA No. 91-141 infringe the Asserted Claims under the Court's Markman Order, Summary Judgment Order, and the reasoning therein, without prejudice to Defendants' right to reinstate their noninfringement defenses upon any remand following appeal of this action;
2. Defendants' "best mode" defense is hereby dismissed without prejudice to reinstate the defense upon any remand following an appeal of this action;
3. Defendants' "enablement" defense is hereby dismissed as it relates to photostability without prejudice to reinstate that aspect of the defense upon any remand following an appeal of this action;
4. Defendants' "impermissible broadening through reexamination" defense is hereby dismissed as it relates to photostability without prejudice to reinstate that aspect of the defense upon any remand following an appeal of this action;
5. During the trial of this matter or in any pre- or post-trial submissions, no party will offer any opinions, arguments, or evidence concerning photostability as it relates to defendants' non-infringement, best mode, or enablement defenses;
6. The parties reserve the right to appeal the Markman Order, the Summary Judgment Order, and the reasoning therein, including, without limitation, the infringement decision, and reserve the right to reinstate any defense referenced herein after any remand; and

7. Dey's claims of infringement concerning unasserted claims of the '344 Patent, the '953 Patent, the '362 Patent, and the '645 Patent are dismissed with prejudice.

Respectfully submitted this 26th day of July, 2013.

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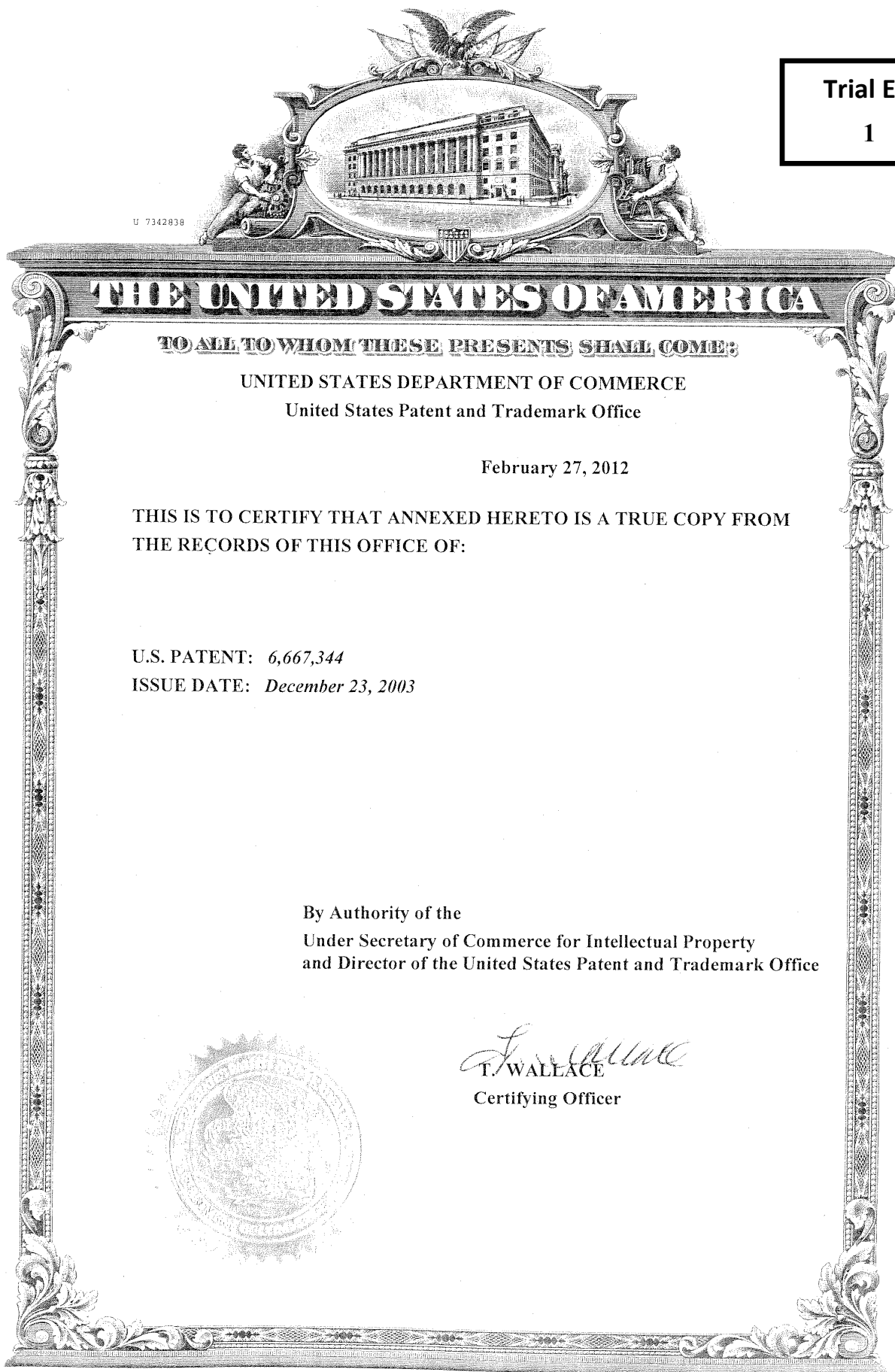
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SO ORDERED this 29th day of July, 2013.


UNITED STATES DISTRICT JUDGE

Case No. 2014-1434

1





US006667344B2

(12) **United States Patent**
Banerjee et al.(10) **Patent No.:** **US 6,667,344 B2**(45) **Date of Patent:** **Dec. 23, 2003**(54) **BRONCHODILATING COMPOSITIONS AND METHODS**(75) Inventors: **Partha S. Banerjee**, Davis, CA (US);
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Imtiaz A. Chaudry, Napa, CA (US)(73) Assignee: **Dey, L.P.**, Napa, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/887,281**(22) Filed: **Jun. 22, 2001**(65) **Prior Publication Data**

US 2002/0151597 A1 Oct. 17, 2002

Related U.S. Application Data

(60) Provisional application No. 60/284,606, filed on Apr. 17, 2001.

(51) Int. Cl.⁷ **A61K 31/35**(52) U.S. Cl. **514/653; 424/45; 424/46**(58) Field of Search **424/45, 46; 514/653**(56) **References Cited****U.S. PATENT DOCUMENTS**

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(57) **ABSTRACT**

Bronchodilating compositions and methods are provided. The compositions are intended for administration as a nebulized aerosol. In certain embodiments, the compositions contain formoterol, or a derivative thereof. Methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders using the compositions provided herein are also provided.

88 Claims, No Drawings

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BRONCHODILATING COMPOSITIONS AND METHODS

RELATED APPLICATIONS

Benefit of priority under 35 U.S.C. §119(e) is claimed to U.S. provisional patent application serial No. 60/284,606; filed Apr. 17, 2001, to Pham et al. The disclosure of the above-referenced application is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

Compositions and methods are provided relating to treatment, prevention, or amelioration of one or more symptoms of broncho-constrictive disorders. In particular, the compositions and methods herein include formoterol, and/or derivatives thereof. The compositions are propellant-free, sterile unit dose or multidose inhalation solutions intended for administration via nebulization.

BACKGROUND OF THE INVENTION

Bronchoconstrictive disorders affect millions worldwide. Such disorders include asthma (including bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness), chronic bronchitis and other chronic obstructive pulmonary diseases. Compounds having β_2 -adrenoreceptor agonist activity have been developed to treat these conditions. Such compounds include, but are not limited to, Albuterol (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); Bambuterol (dimethylcarbamic acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenylene ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methyl-ethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetrahydro-1-((3,4,5-trimethoxyphenyl)methyl)-6,7-isouquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); Fenoterol (5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxy-5-(((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methylethyl)amino)methyl)benzenemethanol); Hexoprenaline (4,4'-(1,6-hexanediyl)-bis(imino(1-hydroxy-2,1-ethanediyl)))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)-butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(2-pyridinyl)ethoxy)hexyl)amino)methyl)benzenemethanol); Pirbuterol (α^6 -(((1,1-dimethylethyl)amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol (((R*,S*)-(\pm))-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolinone); Reproterol ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm))- α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm))-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-

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benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-(((1R)-1-hydroxy-2-(N-((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)-carbostyryl hydrochloride).

These compounds are typically formulated for inhalation therapy. Aqueous or liquid formulations are preferred over solid formulations. Powdered formulations are more difficult to administer, particularly to the young and elderly who are most often the patients in need of such therapy. Compounds, such as formoterol, which has many desirable properties, are not adequately stable in aqueous solutions to be formulated as liquids. Hence there is a need for formulations of compounds, such as formoterol, in a form that can be conveniently administered and that are stable for extended periods of time. Therefore, it is an object herein to provide liquid formulations of β_2 -adrenoreceptor agonist compounds. It is also an object herein to provide more stable formulations of others of these compounds.

SUMMARY OF THE INVENTION

Compositions and methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders are provided. The compositions provided herein are stable solutions of a bronchodilating agent, or a derivative thereof, in a pharmacologically suitable fluid that contains water, that are stable during long term storage. The compositions are suitable for direct administration to a subject in need thereof. Pharmacologically suitable fluids include, but are not limited to, polar fluids, including protic fluids. In certain embodiments herein, the compositions are aqueous solutions.

The compositions provided herein possess an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C. and greater than or equal to 1, 2 or 3 years storage time at 5° C. In certain of these embodiments, using Arrhenius kinetics, >80% or >85% or >90% or >95% estimated bronchodilating agent remains after such storage. These compositions are particularly useful for administration via nebulization. In certain embodiments herein, the subject is a mammal. In other embodiments, the subject is a human.

The compositions provided herein are formulated to remain stable over a relatively long period of time. For example, the compositions provided herein are stored between -15° C. and 25° C., or between 2° C. and 8° C., and remain stable for the desired time. In one embodiment, the compositions are stored at 5° C.

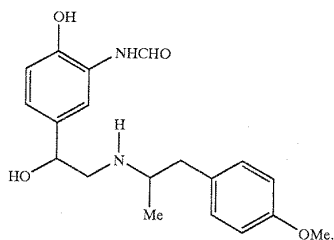
Among the bronchodilating agents for use herein are Albuterol (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); Bambuterol (dimethylcarbamic acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenylene ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetrahydro-1-((3,4,5-trimethoxyphenyl)methyl)-6,7-isouquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); Fenoterol (5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxy-5-(((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methylethyl)amino)methyl)benzenemethanol); Hexoprenaline (4,4'-(1,6-

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hexanediyl)-bis(imino(1-hydroxy-2,1-ethanediyl)))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((methylethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(2-pyridinyl)ethoxy)hexyl)amino)methyl)benzenemethanol); Pirbuterol (α^6 -(((1,1-dimethylethyl)amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol (((R*,S*)-(\pm)-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolinone); Reproterol ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-((1R)-1-hydroxy-2-(N-((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)carbostyryl hydrochloride).

Of particular interest herein is formoterol, having the formula:



Formoterol for use in the compositions and methods provided herein includes 2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof; and also includes the single enantiomers 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide.

In certain embodiments, the compositions are administered via nebulization. Administration of a nebulized aerosol is preferred over the use of dry powders for inhalation in certain subject populations, including pediatric and geriatric groups.

In one embodiment, the compositions for use in the methods provided herein contain a pharmaceutically acceptable derivative of formoterol. In another embodiment, the compositions for use in the methods provided herein contain a pharmaceutically acceptable salt of formoterol. Pharmaceutically acceptable salts include, but are not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. In one embodiment, the compositions for use in the methods provided herein contain formoterol fumarate or formoterol fumarate dihydrate. In another embodiment, the compositions for use in the methods provided herein contain formoterol tartrate.

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Also provided herein are combinations containing a composition provided herein and a nebulizer. The combinations can be packaged as kits, which optionally contain other components, including instructions for use of the nebulizer. Any nebulizer is contemplated for use in the kits and methods provided herein. In particular, the nebulizers for use herein nebulize liquid formulations, including the compositions provided herein, containing no propellant. The nebulizer may produce the nebulized mist by any method known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or vibration. The nebulizer may further have an internal baffle. The internal baffle, together with the housing of the nebulizer, selectively removes large droplets from the mist by impaction and allows the droplets to return to the reservoir. The fine aerosol droplets thus produced are entrained into the lung by the inhaling air/oxygen.

Methods for the treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, including, but not limited to, asthma, including, but not limited to, bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness; chronic bronchitis; and other chronic obstructive pulmonary diseases are provided. The methods involve administering an effective amount of a pharmaceutical composition provided herein to a subject in need of such treatment.

Articles of manufacture, containing packaging material, a composition provided herein, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, are also provided.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, formoterol refers to 2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof. The term formoterol also refers to the single enantiomers 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide.

As used herein, formoterol fumarate refers to a salt of formoterol having the formula (formoterol)- $\frac{1}{2}$ fumarate.

As used herein, formoterol free base refers to the neutral, anhydrous form of formoterol. Thus, a recitation that a composition contains, e.g., 59 μ g/mL of formoterol free base means that the composition contains 59 μ g/mL of neutral, anhydrous formoterol. Such compositions may be prepared using a derivative of formoterol.

As used herein, an aerosol is liquid or particulate matter dispersed in air. Aerosols include dispersions of liquids, including aqueous and other solutions, and solids, including powders, in air.

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As used herein, a nebulized solution refers to a solution that is dispersed in air to form an aerosol. Thus, a nebulized solution is a particular form of an aerosol.

As used herein, a nebulizer is an instrument that is capable of generating very fine liquid droplets for inhalation into the lung. Within this instrument, the nebulizing liquid or solution is atomized into a mist of droplets with a broad size distribution by methods known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or a vibrating orifice. Nebulizers may further contain, eg., a baffle which, along with the housing of the instrument, selectively removes large droplets from the mist by impaction. Thus, the mist inhaled into the lung contains fine aerosol droplets.

As used herein, a pharmacologically suitable fluid is a solvent suitable for pharmaceutical use which is not a liquified propellant gas. Exemplary pharmacologically suitable fluids include polar fluids, including protic fluids such as water.

As used herein, a combination refers to any association between two or among more items.

As used herein, fluid refers to any composition that can flow. Fluids thus encompass compositions that are in the form of semi-solids, pastes, solutions, aqueous mixtures, gels, lotions, creams and other such compositions.

As used herein, a mixture is a mutual incorporation of two or more substances, without chemical union, the physical characteristics of each of the components being retained.

As used herein, the stability of a composition provided herein refers to the length of time at a given temperature that is greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient, e.g., formoterol, is present in the composition. Thus, for example, a composition that is stable for 30 days at 25° C. would have greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient present in the composition at 30 days following storage at 25° C.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chlorprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocy-

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clyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula $C=C(OR)$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula $C=C(OC(OR))$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecule, preferably 1 to about 100, more preferably 1 to about 10, most preferably one to about 2, 3 or 4, solvent or water molecules. Formoterol salts and hydrates are used in certain embodiments herein.

As used herein, treatment means any manner in which one or more of the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating cancer.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, a prodrug is a compound that, upon in vivo administration, is metabolized or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, e.g., Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

It is to be understood that the compounds for use in the compositions and methods provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds for use in the compositions provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization in vivo. Thus, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization in vivo, to administration of the compound in its (S) form.

As used herein, bronchoconstriction refers to a reduction in the caliber of a bronchus or bronchi.

As used herein, undesired and/or uncontrolled bronchoconstriction refers to bronchoconstriction that results in or from a pathological symptom or condition. Pathological conditions include, but are not limited to, asthma and chronic obstructive pulmonary disease (COPD). Pathological symptoms include, but are not limited to, asthma and COPD.

As used herein, the statement that a composition is stable during "long term storage" means that the composition is

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suitable for administration to a subject in need thereof when it has an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C. and greater than or equal to 1, 2 or 3 years storage time at 5° C. In certain embodiments herein, using Arrhenius kinetics, >80% or >85% or >90% or >95% 5 estimated bronchodilating agent remains after such storage.

A. Formoterol

Formoterol (2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide) is derived from adrenaline and, as noted above, is used as a β_2 -stimulator in inhalation therapy of respiratory diseases, particularly for the treatment of bronchial asthma. It has been reported that in patients with reversible obstructive respiratory diseases, formoterol has a bronchodilatory effect. This effect has a relatively rapid onset (approximately 1–3 minutes) and a relatively long duration (greater than 12 hours). Formoterol inhibits the release of leukotrienes and other messenger substances involved with inflammation, such as histamines. In addition, formoterol may bring about a hyperglycaemic activity.

To date, formoterol has been formulated as a dry powder and administered via devices such as the Turbuhaler® and the Aerolizer®. See, e.g., Seberova et al. (2000) *Respir. Med.* 94(6):607–611; Lotvall et al. (1999) *Can. Respir. J.* 6(5): 412–416; Campbell et al. (1999) *Respir. Med.* 93(4): 236–244; Nightingale et al. (1999) *Am. J. Respir. Crit. Care Med.* 159(6):1786–1790; Lecaillon et al. (1999) *Eur. J. Clin. Pharmacol.* 55(2):131–138; Bartow et al. (1998) *Drugs* 55(2):303–322; Ekstrom et al. (1998) *Respir. Med.* 92(8): 1040–1045; Ringdal et al. (1998) *Respir. Med.* 92(8): 1017–1021; Totterman et al. (1998) *Eur. Respir. J.* 12(3): 573–579; Palmqvist et al. (1997) *Eur. Respir. J.* 10(11): 2484–2489; Nielsen et al. (1997) *Eur. Respir. J.* 10(9): 2105–2109; Ullman et al. (1996) *Allergy* 51(10):745–748; Selroos et al. (1996) *Clin. Immunother.* 6:273–299; and Schreurs et al. (1996) *Eur. Respir. J.* 9(8):1678–1683.

Formoterol is also available as a tablet and a dry syrup in certain areas of the world (e.g., Atcock®, marketed by Yamanouchi Pharmaceutical Co. Ltd., Japan). Formoterol formulations are also available in other areas (e.g., Europe and U.S.) for propellant-based metered dose inhalers and dry powder inhalers (e.g., Turbuhaler®, Aerolizer® and Foradil Aerolizer®). None of these formulations are water based. Sterile, stable, aqueous based inhalation solutions of formoterol for nebulization are not available, nor have they been reported.

Compositions containing formoterol in combination with other active ingredients have been disclosed. See, e.g., U.S. Pat. Nos. 6,004,537, 5,972,919 and 5,674,860 (formoterol and budesonide), U.S. Pat. Nos. 5,668,110, 5,683,983, 5,677,280 and 5,654,276 (formoterol and IL-5 inhibitors), U.S. Pat. No. 6,136,603 (formoterol and antisense modulators of IL-5), U.S. Pat. No. 5,602,110 (formoterol and millrinone), U.S. Pat. No. 5,525,623 (formoterol and a tryptase inhibitor), U.S. Pat. Nos. 5,691,336, 5,877,191, 5,929,094, 5,750,549 and 5,780,467 (formoterol and a tachykinin receptor antagonist); and International Patent Application Publication Nos. WO 99/00134 (formoterol and rolfeponide) and WO 99/36095 (formoterol and a dopamine D₂ receptor agonist).

Other compositions containing formoterol have been disclosed in U.S. Pat. Nos. 5,677,809, 6,126,919, 5,733,526, 6,071,971, 6,068,833, 5,795,564, 6,040,344, 6,041,777, 5,874,481, 5,965,622 and 6,161,536.

U.S. Pat. No. 6,150,418 discloses a “liquid active substance concentrate” containing formoterol in the form of its free base or in the form of one of the pharmacologically

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acceptable salts or addition products (adducts) thereof as active substance. This “liquid active substance concentrate” is reported to be a concentrated (i.e., greater than 10 mg/mL, preferably 75 to 500 mg/mL) solution or suspension that is stable for a period of several months possibly up to several years without any deterioration in the pharmaceutical quality. This patent teaches that it is the high concentration that allows for the stability of the concentrate. The “liquid active substance concentrate” is not suitable for direct administration to a patient.

U.S. Pat. No. 6,040,344 discloses an aqueous aerosol formulation of formoterol tartrate for use in a nebulizer. This patent states that the formulation disclosed therein is not attractive for long term storage.

B. Compositions for Use in Treatment, Prevention, or Amelioration of One or More Symptoms of Bronchoconstrictive Disorders

Pharmaceutical compositions containing a β_2 -adrenoreceptor agonist for administration via nebulization are provided. The compositions are sterile filtered and filled in vials, including unit dose vials providing sterile unit dose formulations which are used in a nebulizer and suitably nebulized. Each unit dose vial is sterile and is suitably nebulized without contaminating other vials or the next dose.

The unit dose vials are formed in a form-fill-seal machine or by any other suitable method known to those of skill in the art. The vials may be made of plastic materials that are suitably used in these processes. For example, plastic materials for preparing the unit dose vials include, but are not limited to, low density polyethylene, high density polyethylene, polypropylene and polyesters. In one embodiment, the plastic material is low density polyethylene.

In one embodiment, the β_2 -adrenoreceptor agonist is formoterol, or a pharmaceutically acceptable derivative thereof. In other embodiments, the formoterol for use in the compositions provided herein is formoterol fumarate. Formoterol refers to 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof. The term formoterol also refers herein to the single enantiomers 2-hydroxy-5-(((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)-amino)ethyl)formanilide.

In one embodiment, the compositions contain formoterol free base at a concentration of about 5 μ g/mL to about 2 mg/mL. In other embodiments, the maximum concentration of formoterol free base in the compositions is 1.5 mg/mL. In further embodiments, the concentration of formoterol free base in the compositions is about 10 μ g/mL to about 1 mg/mL, or about 50 μ g/mL to about 200 μ g/mL. In other embodiments, the compositions contain formoterol fumarate at a concentration of about 80 μ g/mL up to about 175 to 200 μ g/mL. In further embodiments, the compositions contain formoterol fumarate at a concentration of about 90 μ g/mL up to about 125 to 150 μ g/mL. The formoterol fumarate is formulated, in certain compositions provided herein, at a concentration of about 100 μ g/mL. The formoterol fumarate is formulated, in other compositions provided herein, at a concentration of about 85 μ g/mL or about 170 μ g/mL. In one embodiment, the formoterol fumarate is formulated for single dosage administration via nebulization at a concentration of about 100 μ g/mL. In another embodiment, the compositions contain formoterol free base at a concentration of about 40 to about 150 μ g/mL, particularly about 59 or about 118 μ g/mL.

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The compositions containing the β_2 -adrenoreceptor agonist, including formoterol, are formulated with a pharmacologically suitable fluid. Pharmacologically suitable fluids include, but are not limited to, polar solvents, including, but not limited to, compounds that contain hydroxyl groups or other polar groups. Such solvents include, but are not limited to, water or alcohols, such as ethanol, isopropanol, and glycols including propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol and polyoxyethylene alcohols.

Polar solvents also include protic solvents, including, but not limited to, water, aqueous saline solutions with one or more pharmaceutically acceptable salt(s), alcohols, glycols or a mixture thereof. For a saline solution as the solvent or as a component thereof, particularly suitable salts are those which display no or only negligible pharmacological activity after administration.

In the embodiments herein, the compositions have a pH of about 2.0 to about 8.0. In other embodiments, the compositions have a pH of about 4.0 to about 6.0, or about 4.5 to about 5.5. In certain of the above embodiments, the compositions are formulated at a pH of about 4, 4.4 or 4.6 up to about 5.5, 5.7 or 6. In other embodiments, the pH is about 5.0. It has been found herein that the rate constant for decomposition of an aqueous solution of formoterol is dependent on pH. The rate constant (k_{obs}) at 60° C. at a pH of 3, 4, 5 and 7 is approximately 0.62, 0.11, 0.044 and 0.55 day⁻¹, respectively. Therefore, the decomposition of formoterol in aqueous solution at 60° C. at a buffer concentration of 5 mM and an ionic strength of 0.05 is slowest at a pH of about 5.0.

The solubility of formoterol in aqueous solution has been found herein to be dependent on pH. Thus, at a pH of between about 5 and about 7, the aqueous solubility of formoterol at ambient temperature is approximately 2.2 mg/mL. At a pH of about 4, the aqueous solubility of formoterol at ambient temperature is approximately 3 mg/mL, while at a pH of about 3, the aqueous solubility of formoterol at ambient temperature is about 4.8 mg/mL. The solubility of formoterol in pure water, for example, high performance liquid chromatography (HPLC) water, at ambient temperature is approximately 2 mg/mL.

In other of the above embodiments, the compositions further contain a buffer, including, but not limited to, citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stauhaugen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), TRIZMA® (tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid)), POPSO (piperazine-N,N'-bis(2-

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hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid)), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanesulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), AMPD (2-amino-2-methyl-1,3-propanediol), and/or any other buffers known to those of skill in the art. In one embodiment, the buffer is citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer. In another embodiment, the buffer is a citrate buffer (citric acid/sodium citrate). The buffer concentration has been found herein to affect the stability of the composition. Buffer concentrations for use herein include from about 0 or 0.01 mM to about 150 mM, or about 1 mM to about 20 mM. In one embodiment, the buffer concentration is about 5 mM. In another embodiment, the buffer concentration is about 1 mM to about 50 mM, or about 20 mM. The kinetic-pH profile of formoterol is dependent on buffer concentration. At low and approximately neutral conditions, increasing the buffer concentration from 5 mM to 20 mM increased the rate constant of decomposition significantly. However, no noticeable differences in rate constant were observed in the pH region of about 4.5 to about 5.5 with increasing buffer concentration from 5 mM to 20 mM. The particular buffer and buffer concentration of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, e.g., the Examples).

The ionic strength of the compositions provided herein also has been found herein to affect the stability of the composition. Ionic strengths of the compositions provided herein are from about 0 to about 0.4, or from about 0.05 to about 0.16. Compositions having a lower ionic strength exhibit improved stability over formulations having higher ionic strength. The rate constant of decomposition was essentially the same at ionic strength 0.05 to 0.1, but increased to some extent at ionic strength of 0.2. The particular ionic strength of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, e.g., the Examples).

In embodiments where the pharmacologically suitable fluid is a saline solution, tonicity adjusting agents may be added to provide the desired ionic strength. Tonicity adjusting agents for use herein include those which display no or only negligible pharmacological activity after administration. Both inorganic and organic tonicity adjusting agents may be used in the compositions provided herein. Tonicity adjusting agents include, but are not limited to, ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate,

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sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethane, uridine and zinc sulfate. In certain embodiments, the tonicity adjusting agent is sodium chloride, which is present at a concentration of from about 0 mg/mL to about 10, 15 or 20 mg/mL. In further embodiments, the compositions contain sodium chloride at a concentration of from about 0 mg/mL to about 7.5 mg/mL. In another embodiment, the compositions contain sodium chloride at a concentration of 0 mg/mL, 1.5 mg/mL, 6.8 mg/mL or 7.5 mg/mL. In these embodiments, the pharmacologically suitable fluid is aqueous saline.

The storage temperature of the compositions provided herein also has been found herein to affect the stability of the composition. Compositions stored at a lower temperature exhibit improved stability over formulations stored at higher temperatures. The effect of temperature on the rate constant of decomposition at pH 5, a buffer concentration of 5 mM, and an ionic strength of 0.05, was linear according to Arrhenius kinetics, i.e., when $\ln k_{obs}$ was plotted against $1/T$, where T is the temperature in degree Kelvin.

The estimated shelf-life of formoterol in the compositions provided herein is significantly greater than that reported for known formoterol compositions. The estimated shelf-life of formoterol in the compositions provided herein is about 6.2 years at 5° C. and about 7.5 months at 25° C. The estimated formoterol concentrations in the compositions provided herein as a function of storage time at 5° C. and usage time at 25° C. was determined. It is estimated that greater than 90% of the initial formoterol present in the composition remains after 3 months of usage time at 25° C. and 3 years of storage time at 5° C. as well as after 0.5 months of usage time at 25° C. and 1 year of storage time at 5° C.

In one embodiment, the compositions provided herein are prepared containing formoterol fumarate at a nominal concentration of 0.1 mg/mL at the indicated pH and citric acid/phosphate buffer concentrations. The solutions were stored at 60° C. In these compositions, formoterol is relatively more stable at a pH from about 4 to about 5, and is also more stable at lower buffer concentration.

The compositions provided herein also may include excipients and additives. The particular excipient or additive for use in the compositions for long term storage provided herein may be determined empirically using methods well known to those of skill in the art (see, e.g., the Examples). Excipients and additives are any pharmacologically suitable and therapeutically useful substance which is not an active substance. Excipients and additives generally have no pharmacological activity, or at least no undesirable pharmacological activity. The excipients and additives include, but are not limited to, surfactants, stabilizers, complexing agents, antioxidants, or preservatives which prolong the duration of use of the finished pharmaceutical formulation, flavorings, vitamins, or other additives known in the art. Complexing agents include, but are not limited to, ethylenediaminetetraacetic acid (EDTA) or a salt thereof, such as the disodium salt, citric acid, nitrilotriacetic acid and the salts thereof. In one embodiment, the complexing agent is EDTA. Preservatives include, but are not limited to, those that protect the solution from contamination with pathogenic particles, including benzalkonium chloride or benzoic acid, or benzoates such as sodium benzoate. Antioxidants include, but are not limited to, vitamins, provitamins, ascorbic acid, vitamin E or salts or esters thereof.

The compositions provided herein also may include a cosolvent, which increases the solubility of additives or the

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active ingredient(s). The particular cosolvent for use in the compositions for long term storage provided herein may be determined empirically using methods well known to those of skill in the art (see, e.g., the Examples). Cosolvents for use herein include, but are not limited to, hydroxylated solvents or other polar solvents, such as alcohols such as isopropyl alcohol, glycols such as propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol, and polyoxyethylene alcohols.

C. Preparation of Compounds for Use in the Compositions

The preparation of the compounds used in the compositions provided herein is described below. Any such compound or similar compound may be synthesized according to a method discussed in general below or by only minor modification of the methods by selecting appropriate starting materials.

Formoterol may be prepared according to the method disclosed in U.S. Pat. No. 3,994,974. Briefly, 4-benzyloxy-3-nitro- α -bromoacetophenone is reacted with N-benzyl-N-(1-methyl-2-p-methoxyphenylethyl)amine to form the α -aminoacetophenone. This compound was subjected to the following series of reactions: (i) reduction of the ketone with sodium borohydride; (ii) reduction of the nitro group with aqueous hydrochloric acid and iron powder; (iii) amine formulation with acetic anhydride and formic acid; and (iv) catalytic reduction over 10% palladium on carbon to afford formoterol free base. Crystallization of the $\frac{1}{2}$ fumarate salt from ethanol provides (formoterol)- $\frac{1}{2}$ fumarate.

The individual enantiomers of formoterol, 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)-formanilide and 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide, may be prepared by the method disclosed in U.S. Pat. No. 6,040,344. Briefly, reaction of optically pure 4-benzyloxy-3-formamidostyrene oxide with an optically pure 4-methoxy- α -methyl-N-(phenylmethyl)benzeneethanamine, followed by debenzilation, affords the desired enantiomer of formoterol. Debenzilation may be accomplished by reduction with hydrogen gas in the presence of a noble metal catalyst, such as palladium on carbon.

The required optically pure 4-benzyloxy-3-formamidostyrene oxide may be prepared from 4-benzyloxy-3-nitro- α -bromoacetophenone by (i) reduction with vorane in the presence of an optically pure aminoindanol, (ii) hydrogenation over platinum oxide catalyst, (iii) formulation with formic acid and acetic anhydride, and (iv) epoxide formation in the presence of potassium carbonate.

The required optically pure 4-methoxy- α -methyl-N-(phenylmethyl)benzeneethanamine may be prepared from 4-methoxyphenylacetone by (i) reductive amination with benzylamine in the presence of hydrogen and a platinum catalyst, and (ii) crystallization of the desired optically pure amine from the resulting racemic mixture as its mandelic acid salt.

D. Formulation of Pharmaceutical Compositions

The compositions provided herein are prepared by procedures well known to those of skill in the art. For example, a formoterol fumarate solution may be prepared by the procedure of EXAMPLE 1. Briefly, a buffer solution having a pH and ionic strength of interest herein is prepared. In one embodiment, the buffer is a mixture of citric acid and sodium citrate, with sodium chloride added to achieve the desired ionic strength. Formoterol fumarate dihydrate is added to the buffer solution with agitation to produce a solution of the desired formoterol concentration. Exemplary

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formoterol concentrations are 0.17 g formoterol fumarate dihydrate/2 L and 0.34 g formoterol fumarate dihydrate/2 L buffer.

E. Evaluation of the Activity of the Compositions

Standard physiological, pharmacological and biochemical procedures are available for testing the compositions provided herein to identify those that possess bronchodilatory activity.

In vitro and in vivo assays that may be used to evaluate bronchodilatory activity are well known to those of skill in the art. See also, e.g., U.S. Pat. Nos. 3,994,974, and 6,068,833; German Patent No. 2,305,092; Kaumann et al. (1985) *Naunyn-Schmied Arch. Pharmacol.* 331:27-39; Lemoine et al. (1985) *Naunyn-Schmied Arch. Pharmacol.* 331:40-51; Tomioka et al. (1981) *Arch. Int. Pharmacodyn.* 250:279-292; Dellamary et al. (2000) *Pharm. Res.* 17(2):168-174; Rico-Mendez et al. (1999) *Rev. Alerg. Mex.* 46(5):130-135; Seberova et al. (2000) *Respir. Med.* 94(6):607-611; Lotvall et al. (1999) *Can. Respir. J.* 6(5):412-416; Campbell et al. (1999) *Respir. Med.* 93(4):236-244; Nightingale et al. (1999) *Am. J. Respir. Crit. Care Med.* 159(6):1786-1790; Lecaillon et al. (1999) *Eur. J. Clin. Pharmacol.* 55(2):131-138; Bartow et al. (1998) *Drugs* 55(2):303-322; Ekstrom et al. (1998) *Respir. Med.* 92(8):1040-1045; Ringdal et al. (1998) *Respir. Med.* 92(8):1017-1021; Totterman et al. (1998) *Eur. Respir. J.* 12(3):573-579; Palmqvist et al. (1997) *Eur. Respir. J.* 10(11):2484-2489; Nielsen et al. (1997) *Eur. Respir. J.* 10(9):2105-2109; Ullman et al. (1996) *Allergy* 51(10):745-748; Selroos et al. (1996) *Clin. Immunother.* 6:273-299; and Schreurs et al. (1996) *Eur. Respir. J.* 9(8):1678-1683.

F. Methods of Treatment of Bronchoconstrictive Disorders

The compositions provided herein are used for treating, preventing, or ameliorating one or more symptoms of a bronchoconstrictive disorders in a subject. In one embodiment, the method includes administering to a subject an effective amount of a composition containing a bronchodilating agent, including, but not limited to, formoterol, whereby the disease or disorder is treated or prevented. The subject treated is, in certain embodiments, a mammal. The mammal treated is, in certain embodiments, a human.

In another embodiment, the method provided herein includes oral administration of a composition provided herein. In certain embodiments herein, the composition is directly administered to a subject in need of such treatment via nebulization without dilution or other modification of the composition prior to administration.

The methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, in another embodiment, further include administering one or more of (a), (b), (c) or (d) as follows: (a) a β_2 -adrenoreceptor agonist; (b) a dopamine (D_2) receptor agonist; (c) a prophylactic therapeutic, such as a steroid; or (d) an anticholinergic agent; simultaneously with, prior to or subsequent to the composition provided herein.

β_2 -Adrenoreceptor agonists for use in combination with the compositions provided herein include, but are not limited to, Albuterol (α^1 -((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); Bambuterol (dimethylcarbamic acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenylene ester); Broxaterol (3-bromo- α -((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetrahydro-1-((3,4,5-trimethoxyphenyl)methyl)-6,

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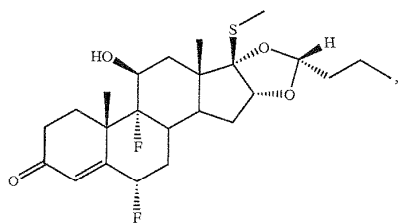
7-isoquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); Fenoterol (5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methylethyl)amino)methyl)benzenemethanol); Hexoprenaline (4,4'-(1,6-hexanediiyl)-bis(imino(1-hydroxy-2,1-ethanediiyl))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(pyridinyl)ethoxy)hexyl)amino)methyl)benzenemethanol); Pirbuterol (α^6 -(((1,1-dimethylethyl)amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol (((R*,S*)-(\pm)-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolinone); Reproterol ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-((1R)-1-hydroxy-2-(N-((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)amino)ethyl)carbostyryl hydrochloride).

Dopamine (D_2) receptor agonists include, but are not limited to, Apomorphine ((r)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo[de,g]quinoline-10,11-diol); Bromocriptine ((5 α)-2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)ergotaman-3',6',18-trione); Cabergoline ((8 β)-N-(3(dimethylamino)propyl)-N-((ethylamino)carbonyl)6-(2-propenyl)ergoline-8-carboxamide); Lisuride (N'-((8 α)-9,10-didehydro-6-methylergolin-8-yl)-N,N-diethylurea); Pergolide ((8 β)-8-((methylthio)methyl)-6-propylergoline); Levodopa (3-hydroxy-L-tryrosine); Pramipexole ((s)-4,5,6,7-tetrahydro-N⁶-propyl-2,6-benzothiazolediamine); Quinpirole hydrochloride (trans-(-)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo [3,4-g]quinoline hydrochloride); Ropinirole (4-(2-(dipropylamino)ethyl)-1,3-dihydro-2H-indol-2-one); and Talipexole (5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thiazolo [4,5-d]azepin-2-amine). Other dopamine D_2 receptor agonists for use herein are disclosed in International Patent Application Publication No. WO 99/36095.

Prophylactic therapeutics for use in combination therapy herein include steroidal anti-inflammatory agents, including, but not limited to, beclomethasone dipropionate (BDP), beclomethasone monopropionate (BMP), flunisolide, triamcinolone acetate, dexamethasone, triptedane, ciclesonid, rofleponide, mometasone, mometasone furoate (Asmanex® Twisthaler™, Shering-Plough Corporation, Kenilworth, N.J.), RPR 106541, having the formula

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fluticasone or fluticasone propionate and budesonide or by way of sodium cromoglycate or nedocromil sodium.

Anticholinergic agents for use herein include, but are not limited to, ipratropium bromide, oxitropium bromide, atropine methyl nitrate, atropine sulfate, ipratropium, belladonna extract, scopolamine, scopolamine methobromide, homatropine methobromide, hyoscyamine, isopropamide, orphenadrine, benzalkonium chloride, tiotropium bromide and glycopyrronium bromide. In certain embodiments, the compositions contain an anticholinergic agent, such as ipratropium bromide or tiotropium bromide, at a concentration of about 5 $\mu\text{g/mL}$ to about 5 mg/mL, or about 50 $\mu\text{g/mL}$ to about 200 $\mu\text{g/mL}$. In other embodiments, the compositions for use in the methods herein contain an anticholinergic agent, including ipratropium bromide and tiotropium bromide, at a concentration of about 83 $\mu\text{g/mL}$ or about 167 $\mu\text{g/mL}$.

Other active ingredients for use herein in combination therapy, include, but are not limited to, IL-5 inhibitors such as those disclosed in U.S. Pat. Nos. 5,668,110, 5,683,983, 5,677,280 and 5,654,276; antisense modulators of IL-5 such as those disclosed in U.S. Pat. No. 6,136,603; milrinone (1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile); milrinone lactate; tryptase inhibitors such as those disclosed in U.S. Pat. No. 5,525,623; tachykinin receptor antagonists such as those disclosed in U.S. Pat. Nos. 5,691,336, 5,877,191, 5,929,094, 5,750,549 and 5,780,467; leukotriene receptor antagonists such as montelukast sodium (Singular[®], R-(E)-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropanecarboxylic acid, monosodium salt), 5-lipoxygenase inhibitors such as zileuton (Zyflo[®], Abbott Laboratories, Abbott Park, Ill.), and anti-IgE antibodies such as Xolair[®] (recombinant humanized anti-IgE monoclonal antibody (CGP 51901; IGE 025A; rhuMAB-E25), Genentech, Inc., South San Francisco, Calif.).

The bronchoconstrictive disorder to be treated, prevented, or whose one or more symptoms are to be ameliorated is associated with asthma, including, but not limited to, bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness; and, particularly in embodiments where an anticholinergic agent is used, other chronic obstructive pulmonary diseases (COPDs), including, but not limited to, chronic bronchitis, emphysema, and associated cor pulmonale (heart disease secondary to disease of the lungs and respiratory system) with pulmonary hypertension, right ventricular hypertrophy and right heart failure. COPD is frequently associated with cigarette smoking, infections, environmental pollution and occupational dust exposure.

G. Nebulizers

The compositions provided herein are intended for administration to a subject in need of such treatment via nebulization. Nebulizers that nebulize liquid formulations contain-

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ing no propellant are suitable for use with the compositions provided herein. Nebulizers are available from, e.g., Pari GmbH (Starnberg, Germany), DeVilbiss Healthcare (Heston, Middlesex, UK), Healthdyne, Vital Signs, Baxter, Allied Health Care, Invacare, Hudson, Omron, Bmed, AirSep, Luminscope, Medisana, Siemens, Aerogen, Mountain Medical, Aerosol Medical Ltd. (Colchester, Essex, UK), AFP Medical (Rugby, Warwickshire, UK), Bard Ltd. (Sunderland, UK), Carri-Med Ltd. (Dorking, UK), Plasm Nuiva (Brescia, Italy), Henleys Medical Supplies (London, UK), Intersurgical (Berkshire, UK), Lifecare Hospital Supplies (Leies, UK), Medic-Aid Ltd. (West Sussex, UK), Medix Ltd. (Essex, UK), Sinclair Medical Ltd. (Surrey, UK), and many others.

Nebulizers for use herein include, but are not limited to, jet nebulizers (optionally sold with compressors), ultrasonic nebulizers, and others. Exemplary jet nebulizers for use herein include Pari LC plus/ProNeb, Pari LC plus/ProNeb Turbo, Pari LC plus/Dura Neb 1000 & 2000, Pari LC plus/Walkhaler, Pari LC plus/Pari Master, Pari LC star, Omron CompAir XL Portable Nebulizer System (NE-C18 and JetAir Disposable nebulizer), Omron CompAir Elite Compressor Nebulizer System (NE-C21 and Elite Air Reusable Nebulizer), Pari LC Plus or Pari LC Star nebulizer with Proneb Ultra compressor, Pulmo-aide, Pulmo-aide LT, Pulmo-aide traveler, Invacare Passport, Inspiration Healthdyne 626, Pulmo-Neb Traverler, DeVilbiss 646, Whisper Jet, Acorn II, Misty-Neb, Allied aerosol, Schuco Home Care, Lexan Plastic Pocet Neb, SideStream Hand Held Neb, Mobil Mist, Up-Draft, Up-Draft II, T Up-Draft, ISO-NEB, AVA-NEB, Micro Mist, and PulmoMate. Exemplary ultrasonic nebulizers for use herein include MicroAir, UltraAir, Siemens Ultra Nebulizer 145, CompAir, Pulmosonic, Scout, 5003 Ultrasonic Neb, 5110 Ultrasonic Neb, 5004 Desk Ultrasonic Nebulizer, Mystique Ultrasonic, Luminscope's Ultrasonic Nebulizer, Medisana Ultrasonic Nebulizer, Microstat Ultrasonic Nebulizer, and MABISMist Hand Held Ultrasonic Nebulizer. Other nebulizers for use herein include 5000 Electromagnetic Neb, 5001 Electromagnetic Neb 5002 Rotary Piston Neb, Lumineb I Piston Nebulizer 5500, Aeroneb[™] Portable Nebulizer System, Aerodose[™] Inhaler, and AeroEclipse Breath Actuated Nebulizer.

H. Articles of Manufacture

The compositions provided herein may be packaged as articles of manufacture containing packaging material, a composition provided herein, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

In one embodiment herein, the compositions are packaged with a nebulizer for direct administration of the composition to a subject in need thereof.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

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EXAMPLE 1

Preparation of Formoterol Inhalation Solution Formulation

To a 5 L stainless steel vessel were added 0.68 g citric acid USP, 1.99 g sodium citrate USP, and 17.5 g sodium chloride USP. Purified water USP (2 L) was added to the stainless steel vessel and the contents were mixed with an overhead stirrer at a speed of 240 rpm for 10 minutes. Formoterol fumarate dihydrate (0.17 g for low dosage strength formulation, 0.34 g for high dosage strength formulation) was added and the solution was stirred at 240 rpm for 90 minutes.

EXAMPLE 2

Preparation of Formoterol Unit Dose Formulations

Following the procedure of EXAMPLE 1, the following formoterol unit dose formulations were prepared.

Low Strength (0.0085%)

A low strength formoterol unit dose formulation was prepared using the following reagents in the amounts indicated: formoterol fumarate dihydrate (0.170 mg), citric acid monohydrate, USP (0.68 mg), sodium citrate dihydrate, USP (1.99 mg), sodium chloride, USP (17.5 mg), and purified water, USP (qs to 2 mL).

High Strength (0.0170%)

A high strength formoterol unit dose formulation was prepared using the following reagents in the amounts indicated: formoterol fumarate dihydrate (0.340 mg), citric acid monohydrate, USP (0.68 mg), sodium citrate dihydrate, USP (1.99 mg), sodium chloride, USP (17.5 mg), and purified water, USP (qs to 2 mL).

EXAMPLE 3

Procedure for Stability Testing of Formoterol Solutions

Stability samples of the solutions prepared in EXAMPLES 1 and 2 were placed in scintillation vials with teflon-lined caps and stored in stability ovens at accelerated temperatures. At selected time points, aliquots of the samples were removed from the scintillation vials. The formoterol concentrations of the samples were analyzed by high performance liquid chromatography.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

What is claimed is:

1. A pharmaceutical composition, comprising formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof.

2. The pharmaceutical composition of claim 1, wherein the composition has an estimated shelf-life of greater than 1 month usage time at 25° C. and greater than or equal to 1 year storage time at 5° C.

3. The pharmaceutical composition of claim 2, wherein greater than about 80% of the initial formoterol is present after 1 month usage time at 25° C. and 1 year storage time at 5° C.

4. The pharmaceutical composition of claim 1 that has been nebulized.

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5. The pharmaceutical composition of claim 1, wherein the pharmacologically suitable fluid comprises a polar solvent.

6. The pharmaceutical composition of claim 5, wherein the polar solvent is a protic solvent.

7. The pharmaceutical composition of claim 6, further comprising a tonicity adjusting agent.

8. The pharmaceutical composition of claim 7, wherein the tonicity adjusting agent is ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine or zinc sulfate.

9. The pharmaceutical composition of claim 8, wherein the tonicity adjusting agent is sodium chloride.

10. The pharmaceutical composition of claim 1, wherein the pharmacologically suitable fluid comprises a buffer.

11. The pharmaceutical composition of claim 10, wherein the buffer is citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid)), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid)), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanedisulfonic acid)), TAPS (N-tris(hydroxy-methyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.

12. The pharmaceutical composition of claim 11, wherein the buffer is citrate buffer.

13. The pharmaceutical composition of claim 12, wherein the buffer concentration is from about 0.01 mM to about 150 mM.

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14. The pharmaceutical composition of claim 13, wherein the buffer concentration is from about 1 mM to about 20 mM.
15. The pharmaceutical composition of claim 14, wherein the buffer concentration is about 5 mM.
16. The pharmaceutical composition of claim 8, wherein the ionic strength of the composition is about 0 to about 0.4.
17. The pharmaceutical composition of claim 16, wherein the ionic strength of the composition is about 0.05 to about 0.16.
18. The pharmaceutical composition of claim 1, wherein the pH of the composition is about 2.0 to about 8.0.
19. The pharmaceutical composition of claim 18, wherein the pH of the composition is about 4.0 to about 6.0.
20. The pharmaceutical composition of claim 19, wherein the pH of the composition is about 4.5 to about 5.5.
21. The pharmaceutical composition of claim 20, wherein the pH of the composition is about 5.0.
22. The pharmaceutical composition of claim 1, wherein the formoterol free base concentration is about 5 $\mu\text{g/mL}$ to about 2 mg/mL.
23. The pharmaceutical composition of claim 22, wherein the formoterol free base concentration is about 10 $\mu\text{g/mL}$ to about 1 mg/mL.
24. The pharmaceutical composition of claim 23, wherein the formoterol free base concentration is about 50 $\mu\text{g/mL}$ to about 200 $\mu\text{g/mL}$.
25. The pharmaceutical composition of claim 24, wherein the formoterol free base concentration is about 59 $\mu\text{g/mL}$.
26. The pharmaceutical composition of claim 24, wherein the formoterol free base concentration is about 118 $\mu\text{g/mL}$.
27. The pharmaceutical composition of claim 8, further comprising a buffer.
28. The pharmaceutical composition of claim 27, wherein the buffer is citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanedisulfonic acid)), TAPS (N-tris(hydroxy-methyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.
29. The pharmaceutical composition of claim 28, wherein the buffer is citrate buffer.
30. The pharmaceutical composition of claim 29, wherein the buffer concentration is from about 0.01 mM to about 150 mM.

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31. The pharmaceutical composition of claim 30, wherein the buffer concentration is from about 1 mM to about 20 mM.
32. The pharmaceutical composition of claim 31, wherein the buffer concentration is about 5 mM.
33. The pharmaceutical composition of claim 27, wherein the ionic strength of the composition is about 0 to about 0.4.
34. The pharmaceutical composition of claim 33, wherein the ionic strength of the composition is about 0.05 to about 0.16.
35. The pharmaceutical composition of claim 27, wherein the pH of the composition is about 2.0 to about 8.0.
36. The pharmaceutical composition of claim 35, wherein the pH of the composition is about 4.0 to about 6.0.
37. The pharmaceutical composition of claim 36, wherein the pH of the composition is about 4.5 to about 5.5.
38. The pharmaceutical composition of claim 37, wherein the pH of the composition is about 5.0.
39. The pharmaceutical composition of claim 27, wherein the formoterol free base concentration is about 5 $\mu\text{g/mL}$ to about 2 mg/mL.
40. The pharmaceutical composition of claim 39, wherein the formoterol free base concentration is about 10 $\mu\text{g/mL}$ to about 1 mg/mL.
41. The pharmaceutical composition of claim 40, wherein the formoterol free base concentration is about 50 $\mu\text{g/mL}$ to about 200 $\mu\text{g/mL}$.
42. The pharmaceutical composition of claim 41, wherein the formoterol free base concentration is about 59 $\mu\text{g/mL}$.
43. The pharmaceutical composition of claim 41, wherein the formoterol free base concentration is about 118 $\mu\text{g/mL}$.
44. The pharmaceutical composition of claim 25 that has been nebulized.
45. The pharmaceutical composition of claim 26 that has been nebulized.
46. The pharmaceutical composition of claim 42 that has been nebulized.
47. The pharmaceutical composition of claim 43 that has been nebulized.
48. The pharmaceutical composition of claim 27 that has been nebulized.
49. The pharmaceutical composition of claim 42, wherein the buffer is citrate buffer.
50. The pharmaceutical composition of claim 42, wherein the buffer concentration is about 5 mM.
51. The pharmaceutical composition of claim 42, wherein the ionic strength of the composition is about 0.05 to about 0.16.
52. The pharmaceutical composition of claim 42, wherein the pH of the composition is about 5.0.
53. The pharmaceutical composition of claim 42, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.
54. The pharmaceutical composition of claim 43, wherein the buffer is citrate buffer.
55. The pharmaceutical composition of claim 43, wherein the buffer concentration is about 5 mM.
56. The pharmaceutical composition of claim 43, wherein the ionic strength of the composition is about 0.05 to about 0.16.
57. The pharmaceutical composition of claim 43, wherein the pH of the composition is about 5.0.
58. The pharmaceutical composition of claim 43, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

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59. The pharmaceutical composition of claim 53 that has been nebulized.

60. The pharmaceutical composition of claim 58 that has been nebulized.

61. A nebulized solution, comprising formoterol or a derivative thereof in a pharmacologically suitable fluid.

62. A combination, comprising:

(a) the pharmaceutical composition of claim 1 formulated for single dosage administration; and

(b) a vial.

63. The combination of claim 62, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

64. The combination of claim 62, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

65. An article of manufacture, comprising packaging material, an aqueous composition comprising the composition of claim 1 formulated for single dosage administration, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

66. An article of manufacture, comprising packaging material, the composition of claim 53 formulated for single dosage administration, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

67. An article of manufacture, comprising packaging material, the composition of claim 58 formulated for single dosage administration, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

68. The pharmaceutical composition of claim 1, further comprising one or more of (a) to (j) as follows: (a) a β_2 -adrenoreceptor agonist; (b) a dopamine (D_2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lipoxygenase inhibitor; or (j) an anti-IgE antibody.

69. The pharmaceutical composition of claim 11, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

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70. The pharmaceutical composition of claim 27, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

71. The pharmaceutical composition of claim 13, wherein the buffer concentration is from about 1 mM to about 50 mM.

72. The pharmaceutical composition of claim 71, wherein the buffer concentration is about 20 mM.

73. The pharmaceutical composition of claim 30, wherein the buffer concentration is from about 1 mM to about 50 mM.

74. The pharmaceutical composition of claim 73, wherein the buffer concentration is about 20 mM.

75. The pharmaceutical composition of claim 42, wherein the buffer concentration is about 20 mM.

76. The pharmaceutical composition of claim 42, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

77. The pharmaceutical composition of claim 43, wherein the buffer concentration is about 20 mM.

78. The pharmaceutical composition of claim 43, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

79. The pharmaceutical composition of claim 76 that has been nebulized.

80. The pharmaceutical composition of claim 78 that has been nebulized.

81. The combination of claim 62, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

82. The combination of claim 62, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

83. The pharmaceutical composition of claim 1, further comprising an anticholinergic agent.

84. The pharmaceutical composition of claim 83, wherein the anticholinergic agent is ipratropium bromide, oxitropium bromide, atropine methyl nitrate, tiotropium bromide or glycopyrronium bromide.

85. The pharmaceutical composition of claim 84, wherein the anticholinergic agent is ipratropium bromide.

86. The pharmaceutical composition of claim 85, wherein the ipratropium bromide is present at a concentration of about 5 $\mu\text{g/mL}$ to about 5 mg/mL.

87. The pharmaceutical composition of claim 84, wherein the anticholinergic agent is tiotropium bromide.

88. The pharmaceutical composition of claim 85, wherein the tiotropium bromide is present at a concentration of about 5 $\mu\text{g/mL}$ to about 5 mg/mL.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,667,344 B2
DATED : December 23, 2003
INVENTOR(S) : Banerjee et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

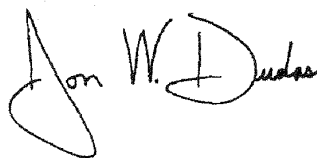
Title page.

Item [56], **References Cited**, OTHER PUBLICATIONS, please add the following:

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Signed and Sealed this

Twentieth Day of April, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,667,344 B2
APPLICATION NO. : 09/887281
DATED : December 23, 2003
INVENTOR(S) : Partha S. Banerjee et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 1, claim number 1, line number 31, "pharmecutical" should be changed to
--pharmaceutical--;

At column 1, claim number 1, line number 35, "effect" should be changed to --effective--.

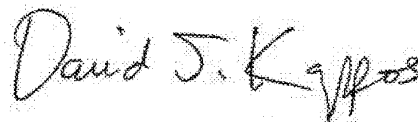
At column 3, claim number 102, line number 8, "citratric" should be changed to --citric--;

At column 3, claim number 106, line number 26, "wherein the formoterol" should be changed to
wherein --said-- formoterol;

At column 3, claim number 106, line number 27, "stereoisomer optically" should be changed to
stereoisomer --is-- optically;

At column 3, claim number 109, line number 45-46, "tartate" should be changed to --a tartrate--.

Signed and Sealed this
Third Day of January, 2012



David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

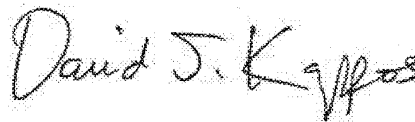
PATENT NO. : 6,667,344 B2
APPLICATION NO. : 09/887281
DATED : December 23, 2003
INVENTOR(S) : Partha S. Banerjee et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

This certificate supersedes the Certificate of Correction issued January 12, 2012. The certificate is vacated since errors appearing on the Certificate of Correction does not correspond to text in the printed patent. The Certificate of Correction should not have been issued.

Signed and Sealed this
Thirty-first Day of January, 2012



David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,667,344 C1
APPLICATION NO. : 90/010488
DATED : October 11, 2011
INVENTOR(S) : Partha S. Banerjee et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 1, claim number 1, line number 31, "pharmecutical" should be changed to
--pharmaceutical--;

At column 1, claim number 1, line number 35, "effect" should be changed to --effective--.

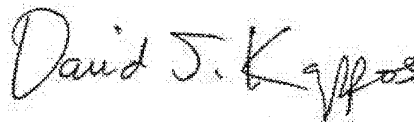
At column 3, claim number 102, line number 8, "citratric" should be changed to --citric--;

At column 3, claim number 106, line number 26, "wherein the formoterol" should be changed to
wherein --said-- formoterol;

At column 3, claim number 106, line number 27, "stereoisomer optically" should be changed to
stereoisomer --is-- optically;

At column 3, claim number 109, line number 45-46, "tartate" should be changed to --a tartrate--.

Signed and Sealed this
Seventh Day of February, 2012



David J. Kappos
Director of the United States Patent and Trademark Office



US00667344C1

(12) **EX PARTE REEXAMINATION CERTIFICATE** (8624th)**United States Patent****Banerjee et al.**(10) **Number:** **US 6,667,344 C1**(45) **Certificate Issued:** **Oct. 11, 2011**(54) **BRONCHODILATING COMPOSITIONS AND METHODS**(75) **Inventors:** **Partha S. Banerjee**, Davis, CA (US);
Stephen Pham, Sacramento, CA (US);
Samuel O. Akapo, Vacaville, CA (US);
Imtiaz A. Chaudry, Napa, CA (US)(73) **Assignee:** **JPMorgan Chase Bank, N.A.**, Chicago, IL (US)**Reexamination Request:**

No. 90/010,488, May 11, 2009

Reexamination Certificate for:Patent No.: **6,667,344**
Issued: **Dec. 23, 2003**
Appl. No.: **09/887,281**
Filed: **Jun. 22, 2001**

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Certificate of Correction issued Apr. 20, 2004.

Related U.S. Application Data

(60) Provisional application No. 60/284,606, filed on Apr. 17, 2001.

(51) **Int. Cl.**

A61K 9/12	(2006.01)
A61K 9/00	(2006.01)
A61K 31/135	(2006.01)
A61K 31/16	(2006.01)
A61K 31/165	(2006.01)
A61K 31/167	(2006.01)
A61K 31/35	(2006.01)
A61K 31/375	(2006.01)
A61K 31/444	(2006.01)
A61K 31/46	(2006.01)
A61K 31/56	(2006.01)
A61K 31/58	(2006.01)
A61K 39/395	(2006.01)
A61K 45/00	(2006.01)
A61K 47/04	(2006.01)
A61K 47/10	(2006.01)
A61K 47/12	(2006.01)
A61K 47/16	(2006.01)
A61K 47/18	(2006.01)
A61K 47/22	(2006.01)
A61K 47/26	(2006.01)
A61K 47/38	(2006.01)
A61K 31/4427	(2006.01)
A61K 47/02	(2006.01)
A61L 9/04	(2006.01)
A61P 11/06	(2006.01)
A61P 11/08	(2006.01)
A61P 11/00	(2006.01)

(52) **U.S. Cl.** 514/653; 424/45; 424/46(58) **Field of Classification Search** None
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Dwayne Jones(57) **ABSTRACT**

Bronchodilating compositions and methods are provided. The compositions are intended for administration as a nebulized aerosol. In certain embodiments, the compositions contain formoterol, or a derivative thereof. Methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders using the compositions provided herein are also provided.

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Page 2

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- U.S. Appl. No. 09/887,496: Non-Final Office Action dated Apr. 24, 2002, 7 pages.
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- U.S. Appl. No. 09/887,496: Non-Final Office Action dated Aug. 27, 2007, 15 pages.
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- U.S. Appl. No. 09/887,496: Supplemental Advisory Action dated Dec. 19, 2003, 2 pages.
- U.S. Appl. No. 10/145,978: Final Office Action dated May 12, 2004, 8 pages.
- U.S. Appl. No. 10/145,978: Final Office Action dated Jan. 3, 2008, 11 pages.
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- Docket Sheet dated Aug. 8, 2010 in *Dey v. Teva* in the United States District Court for the Northern District of West Virginia, Civil Action No. 1:09-cv-00087, Jun. 23, 2009.
- Dey's Complaint in *Dey v. Teva* in the United States District Court for the Northern District of West Virginia, Civil Action No. 1:09-cv-00087.
- Teva's Answer in *Dey v. Teva* in the United States District Court for the Northern District of West Virginia, Civil Action No. 1:09-cv-00087.
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- Letter of May 12, 2009 from Teva Parenteral to Dey L.P.: Notice of ANA 91-141 Concerning Formoterol Fumarate Inhalation Solution, 0.02 mg/2 mL, With Paragraph IV Certification Concerning U.S. Patent Nos. 6,667,344, 6,814,953, 7,348,362 and 7,462,645 (Teva) [Teva Confidential—Filed Under Seal].
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Supplemental Complaint in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, Mar. 30, 2009 (Dey).

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Mylan's Reply to Sepracor's Amended Answer and Counterclaims to Dey's Supplemental Complaint in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, May 7, 2009 (Dey) [Dey Confidential—Filed Under Seal].

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Dey's Reply to Sepracor's Answer and Counterclaims to Dey's Second Supplemental Complaint in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, Jul. 8, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Mylan's Reply to Sepracor's Answer and Counterclaims to Dey's Second Supplemental Complaint in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, Jul. 8, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Dey's Supplemental Objections and Responses to Sepracor's First Set of Interrogatories to Dey in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Dey's Objections and Responses to Sepracor's First Set of Interrogatories in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Dey and Mylan's Objections and Responses to Sepracor's Third Set of Interrogatories in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, (Dey) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron, Sep. 25, 2009 (Sepracor) [Dey Confidential—Filed Under Seal] [Sepracor Confidential—Redacted] [Ok].

Opening Expert Report of Peter Byron Exhibit 1: Curriculum Vitae of Peter Byron (Sepracor).

Opening Expert Report of Peter Byron Exhibit 2: List of Documents Considered (Sepracor).

Opening Expert Report of Peter Byron Exhibit 3: U.S. Patent No. 6,667,344 (currently under reexamination, Control No. 90/010,488) (provided as Document A129).

Opening Expert Report of Peter Byron Exhibit 4: U.S. Patent No. 6,814,953 (currently under reexamination, Control No. 90/010,489) (provided as Document A133).

Opening Expert Report of Peter Byron Exhibit 5: U.S. Patent No. 7,348,362 (provided as Document A136).

Opening Expert Report of Peter Byron Exhibit 6: U.S. Patent No. 7,462,645 (provided as Document A137).

Opening Expert Report of Peter Byron Exhibit 7: U.S. Patent No. 7,465,756 (provided as Document A138).

Opening Expert Report of Peter Byron Exhibit 8: U.S. Patent No. 7,473,710 (provided as Document A139).

Opening Expert Report of Peter Byron Exhibit 9: U.S. Patent No. 7,541,385 (provided as Document A140).

Opening Expert Report of Peter Byron Exhibit 10: U.S. Patent No. 3,994,974 (provided as Document A23).

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Opening Expert Report of Peter Byron Exhibit 14: *Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*. (ed. by Martin, A.), Fourth edition, pp. 147, 178–186, 284–317 (1993).

Opening Expert Report of Peter Byron Exhibit 15: Pharmaceutical Development Report for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 16: PCT Publication WO 01/39745 (provided as Document B59).

Opening Expert Report of Peter Byron Exhibit 17: U.S. Patent No. 6,667,344 (provided as Document A129).

Opening Expert Report of Peter Byron Exhibit 18: Response to Office Action, dated Apr. 22, 2003 in U.S. Appl. No. 09/887,281.

Opening Expert Report of Peter Byron Exhibit 19: Summary of Formoterol work done by M. Joyce (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 20: U.S. Patent No. 6,150,418 (provided as Document A93).

Opening Expert Report of Peter Byron Exhibit 21: Lachman, L., et al., *The Theory and Practice of Industrial Pharmacy*. (Third edition, pp. 176, 191–193, 761–770) (1986).

Opening Expert Report of Peter Byron Exhibit 22: Summary of Formoterol Unit Dose Formulation Development (Sepracor) [Dey Confidential—Filed Under Seal].

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Opening Expert Report of Peter Byron Exhibit 23: First Banerjee Deposition Transcript, Feb. 13, 2009 (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 24: Oral Inhalation PDT Meeting Minutes Nov. 9, 2000 (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 25: U.S. Patent No. 6,161,536 (provided as Document A95).

Opening Expert Report of Peter Byron Exhibit 26: Effect Of Surfactants And Cosolvents On Formoterol Stability (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 27: A Comparative Stability Study Of Formoterol In Active Substance Concentrate (U.S. Patent #6,150,418) And Dey's Formoterol Fumarate Inhalation Solutions (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 28: Akapo Deposition Transcript, Dec. 10, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 29: Letter of May 12, 2009 from Teva Parenteral to Dey L.P.: Notice of ANA 91-141 Concerning Formoterol Fumarate Inhalation Solution, 0.02 mg/2 mL, With Paragraph IV Certification Concerning U.S. Patent Nos. 6,667,344, 6,814,953, 7,348, 362 and 7,462,645 (Teva) [Teva Confidential—Filed Under Seal].

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Opening Expert Report of Peter Byron Exhibit 36: Formoterol Unit Dose Preliminary Results and Formulation Plan. (Sepracor) [Dey Confidential—Filed Under Seal].

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Opening Expert Report of Peter Byron Exhibit 39: Decision on Petition dated Oct. 8, 2002 in U.S. Appl. No. 09/887,281.

Opening Expert Report of Peter Byron Exhibit 40: Table Comparing the Claims of the '344 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 41: Table Comparing the Claims of the '953 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 42: Table Comparing the Claims of the '362 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 43: Table Comparing the Claims of the '385 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 44: Table Comparing the Claims of the '645 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 45: Table Comparing the Claims of the '710 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 46: Table Comparing the Claims of the '756 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 47: Rosenberg, J., et al., *Mass Balance and Metabolism of [³H] Formoterol in Healthy Men After Combined I.V. and Oral Administration Mimicking Inhalation*. Drug Metabolism and Disposition 27(10): 1104-1116 (1999).

Opening Expert Report of Peter Byron Exhibit 48: Formoterol Fumarate Formulation Activities (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 49: (Sepracor) [Dey Confidential—Filed Under Seal] Missing Still Need Document.

Opening Expert Report of Peter Byron Exhibit 50: Laskar Deposition Transcript, Sep. 11, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 51: (Sepracor) [Sepracor Confidential—Copy Not Available].

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Opening Expert Report of Peter Byron Exhibit 80: Dey's Supplemental Objections and Responses to Sepracor's First Set of Interrogatories to Dey. (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 91: Dey's and Mylan's Objections and Responses to Sepracor's Third Set of Interrogatories. (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 97: Second Chaudry Deposition Transcript, Jul. 1, 2009. (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 98: Formoterol, Formoterol Concentrate, and Formoterol Low Volume Pls (also cited as Document D. (Carpenter Exh 114) (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 99: Declaration of P. Banerjee dated Sep 24, 2004 submitted in U.S. Appl. No. 09/887,496.

Rebuttal Expert Report of Peter Byron, Oct. 23, 2009 (Sepracor) [Dey Confidential—Filed Under Seal] [Sepracor Confidential—Redacted].

Rebuttal Expert Report of Peter Byron Exhibit 100: Amendment After Final dated Apr. 22, 2003, submitted in U.S. Appl. No. 09/887,281.

Rebuttal Expert Report of Peter Byron Exhibit 101: Notice of Allowance.

Rebuttal Expert Report of Peter Byron Exhibit 102: Akapo Deposition Transcript, Dec. 10, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

Rebuttal Expert Report of Peter Byron Exhibit 103: Laskar Deposition Transcript, Sep. 11, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

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Rebuttal Expert Report of Peter Byron Exhibit 104: Second Chaudry Deposition Transcript, Ju. 1, 2009 (Sepracor) [Dey Confidential—Filed Under Seal].

Rebuttal Expert Report of Peter Byron Exhibit 105: United States Pharmacopeia, pp. 2–14 (1999).

Reply Expert Report of Peter Byron Nov. 20, 2009 (Sepracor) [Dey Confidential—Filed Under Seal] [Sepracor Confidential—Redacted].

Reply Expert Report of Peter Byron Exhibit 107: Cohen, S.P., et al., *Nebulized Morphine as a Treatment for Dyspnea in a Child with Cystic Fibrosis*. Pediatrics, 2002; vol. 110, No. 3, Sep. 2002.

Reply Expert Report of Peter Byron Exhibit 108: Foral, P.A., et al., *Nebulized Opioids Use in COPD*. Chest 125:691–694 (2004).

Reply Expert Report of Peter Byron Exhibit 109: Second Chaudry Deposition Transcript, Jul. 1, 2009 (Sepracor) [Dey Confidential—Filed Under Seal].

Reply Expert Report of Peter Byron Exhibit 110: Laskar Deposition Transcript, Sep. 11, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

Reply Expert Report of Peter Byron Exhibit 111: Amendment dated Mar. 23, 2007 submitted in U.S. Appl. No. 10/887,785.

Reply Expert Report of Peter Byron Exhibit 112: Rieger Deposition Transcript, Aug. 19, 2009 (Sepracor) [Dey Confidential—Filed Under Seal].

Reply Expert Report of Peter Byron Exhibit 113: Fluorouracil® Package Insert.

Reply Expert Report of Peter Byron Exhibit 114: Buffered Pfizerpen® Instructions.

Reply Expert Report of Peter Byron Exhibit 115: Interoffice Memo from G. Michaud to M. Engle, Apr. 4, 2002 (Sepracor) [Dey Confidential—Filed Under Seal].

Reply Expert Report of Peter Byron Exhibit 118: Akapo Deposition Transcript, Dec. 10, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron—noted in Exhibit 2: Handbook of Pharmaceutical Excipients, 3rd Ed., (ed. Kibbe, A.H.), “Citric Acid Monohydrate,” pp. 140–142 (2000) (provided as document C43) (copy not available—will supply in Supplemental IDS).

Expert Report of Dr. Gene Colice, Nov. 20, 2009 (Dey).

Expert Report of Dr. Gene Colice Exhibit 1: Curriculum Vitae for Dr. Gene Colice (Dey).

Expert Report of Dr. Gene Colice Exhibit 2: Testifying Case List for Dr. Gene Colice (Dey).

Expert Report of Dr. Gene Colice Exhibit 3: List of Documents Considered (Dey).

Expert Report of Dr. Gene Colice Exhibit 4: Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease—Update 2008.

Expert Report of Dr. Gene Colice Exhibit 5: Dolovich et al., *Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines*. Chest 2005; 127: 335–371.

Expert Report of Dr. Gene Colice Exhibit 6: Nebulizers—Perforomist and Brovana—Coverage Criteria and Billing Instructions. TriCenturion Bulletin, Aug. 2007.

Expert Report of Hon. Gerald Mossinghoff, Oct. 23, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Expert Report of Hon. Gerald Mossinghoff Exhibit A: Curriculum Vitae for Hon. Gerald Mossinghoff (Dey).

Expert Report of Hon. Gerald Mossinghoff Exhibit B: Publications of Hon. Gerald Mossinghoff (Dey).

Expert Report of Hon. Gerald Mossinghoff Exhibit C: The Hon. Gerald Mossinghoff Appeared as a Principal Witness in the Following Congressional Hearings (Dey).

Expert Report of Hon. Gerald Mossinghoff Exhibit D: Patent Cases in which the Hon. Gerald Mossinghoff Testified as an Expert Witness in Court or in a Deposition (Dey).

Expert Report of Hon. Gerald Mossinghoff Exhibit E: List of Documents Considered (Dey).

Expert Report of Hon. Gerald Mossinghoff—noted in Exhibit E: Letter from Jeffery Alan Hovden to David M. Conca, Jul. 22, 2008.

Rebuttal Expert Report of Lehrman, Oct. 22, 2009 [Sepracor Confidential—Redacted] [Dey Confidential—Filed Under Seal].

Rebuttal Expert Report of Lehrman Exhibit 1: List of Documents Considered.

Rebuttal Expert Report of Lehrman Exhibit 2: Maesen, F.P.V., et al., *Formoterol Suspension Aerosol Comparison with Formoterol Solution Aerosol for 12 Weeks in Asthmatic Patients*. Chest 102:1544–1549 (1992) (provided as Document C45).

Rebuttal Expert Report of Lehrman Exhibit 3: U.S. Patent No. 6,150,418 (provided as Document A93).

Rebuttal Expert Report of Lehrman Exhibit 4: A Comparative Stability Study Of Formoterol In Active Substance Concentrate (US Patent #6,150,418 [to Hochrainer et al.]) and Dey's Formoterol Fumarate Inhalation Solutions Oct. 10, 2005 [Dey Confidential—Filed Under Seal].

Rebuttal Expert Report of Lehrman Exhibit 5: Declaration of P. Banerjee dated Sep. 24, 2004 submitted in U.S. Appl. No. 09/887,496 (Dey).

Rebuttal Expert Report of Lehrman Exhibit 6: U.S. Patent No. 3,994,974 (provided as Document A23).

Rebuttal Expert Report of Lehrman Exhibit 7: U.S. Patent No. 6,040,344 (provided as Document A85).

Rebuttal Expert Report of Lehrman Exhibit 8: Guidance for Industry: Analytical Procedures and Methods Validation—Draft Guidance, Aug. 2000.

Rebuttal Expert Report of Lehrman Exhibit 9: NDA Analytical Procedures (Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL (Dey) [Dey Confidential—Filed Under Seal].

Rebuttal Expert Report of Lehrman Exhibit 12: Foradil®.

Rebuttal Expert Report of Lehrman Exhibit 13: European Patent No. 1 157 689 (provided as Document B7).

Rebuttal Expert Report of Lehrman Exhibit 14: Formoterol Inhalation Unit Dose (Dey) [Dey Confidential—Filed Under Seal].

Expert Report of Robert Kuhn, Oct. 23, 2009 (Dey) Expert Report Not Under Seal? FLH Marks as Public?. See D164.

Expert Report of Robert Kuhn Exhibit 1: U.S. Patent No. 3,994,974 (provided as Document A23).

Expert Report of Robert Kuhn Exhibit 2: Curriculum Vitae for Robert Kuhn (Dey).

Expert Report of Robert Kuhn Exhibit 3: List of Materials Reviewed (Dey).

Expert Report of Robert Kuhn Exhibit 4: Kuhn, R., *Formulation of Aerosolized Therapeutics* Chest 120 (2001) 94S–98S.

Expert Report of Robert Kuhn Exhibit 5: Guhan et al., *Systemic effects of formoterol and salmeterol: a dose-response comparison in healthy subjects*. Thorax 55 (2000) 650–656.

Expert Report of Robert Kuhn Exhibit 6: Kuhn, R., *Pharmaceutical Considerations in Aerosol Drug Delivery* Pharmacotherapy 22 (2002) 80S–85S.

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- Expert Report of Robert Kuhn Exhibit 7: Walsh, *Pharmaceutical Biotechnology: Concepts and Applications*, John Wiley & Sons, Ltd., West Sussex, England, 2007, p. 72.
- Expert Report of Robert Kuhn Exhibit 8: Hickey, A.J., *Pharmaceutical Inhalation Aerosol Technology*, Marcel Dekker Inc., New York, Ed. 2, 2004, p. 282.
- Expert Report of Robert Kuhn Exhibit 9: FDA CDER Transcript, Meeting of Pharmacy Compounding Advisory Committee, Sep. 14, 1998, p. 136–139.
- Expert Report of Robert Kuhn Exhibit 10: Molema et al., *Drug Targeting Organ-Specific Strategies*, Wiley-VCH, New York, 2001, p. 67.
- Expert Report of Robert Kuhn Exhibit 11: Ganderton et al., *Drug Delivery to the Respiratory Tract*, Ellis Horwood Ltd., Chichester, England, 1987, p. 128.
- Expert Report of Robert Kuhn Exhibit 12: Garg et al., *Insulin Delivery via Lungs—Is It Still Possible?* Diabetes Technology & Therapeutics 11, Suppl. 2 (2009) S–I.
- Opening Expert Report of Larry Nixon, Sep. 25, 2009—(Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Larry Nixon Exhibit 1: Documents Considered.
- Opening Expert Report of Larry Nixon Exhibit 2: Curriculum Vitae for Larry Nixon.
- Reply Expert Report of Larry Nixon, Nov. 20, 2009 (Sepracor) [Dey Confidential—Filed Under Seal].
- Reply Expert Report of Larry Nixon Exhibit 1: United States Patent and Trademark Office Utility, Plant, and Reissue Examiner Staffing FY 2009.
- Reply Expert Report of Larry Nixon Exhibit 2: List of Documents Considered.
- Reply Expert Report of Larry Nixon Exhibit 3: United States Patent and Trademark Office Performance and Accountability Report FY 2009.
- Opening Expert Report of Dr. Philip Marcus, Oct. 23, 2009 (Sepracor).
- Opening Expert Report of Dr. Philip Marcus Exhibit 1: Curriculum Vitae for Dr. Philip Marcus.
- Opening Expert Report of Dr. Philip Marcus Exhibit 2: Cases Testified in over the last Four Years.
- Opening Expert Report of Dr. Philip Marcus Exhibit 3: List of Documents Considered.
- Opening Expert Report of Dr. Philip Marcus Document Reviewed: Dolovich, M.B., et al., *Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines*. Chest 127:335–371 (2005).
- Opening Expert Report of Dr. Philip Marcus Document Reviewed: Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease—Updated 2008.
- Opening Expert Report of Dr. Philip Marcus Document Reviewed: Standards for the Diagnosis and Management of Patients with COPD (2004).
- Reply Expert Report of Dr. Philip Marcus, Nov. 20, 2009.
- Reply Expert Report of Dr. Philip Marcus Exhibit 1: List of Documents Considered.
- Supplemental Expert Report of Dr. Gordon Rausser, PhD, Oct. 22, 2009 (Dey) [Dey Confidential—Filed Under Seal].
- Supplemental Expert Report of Dr. Gordon Rausser Exhibit A: Four Year Testimony List of Gordon Rausser (Dey).
- Supplemental Expert Report of Dr. Gordon Rausser Exhibit B: Additional Materials Reviewed and Relied On (Dey).
- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Label for Perforomist.
- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Label for Brovana.
- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Grove, C., *Availability of Xopenex and Brovana for Medicare Patients*, Associated Content, Sep. 17, 2007, www.associatedcontent.com/article/372751/availability_of_xopenex_and_brovana.html?cat=71 (last visited Jul. 26, 2010).
- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Medpac, Report to the Congress. *Variation and innovation in Medicare. Chapter 9: Medicare payments for outpatient drugs under Part B*, Jun. 2003, pp. 149–170.
- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: NHIC Corp., *Nebulizers—Brovana and Perforomist—instructions for new HCPCS codes: Apr. 17, 2008*, www.medicarenhic.com/dme/medical_review/mr_bulletins/mr_bulletin_current/041708_neb.pdf (last visited Jul. 26, 2010).
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- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: American Association for Respiratory Care, *AARC Seeks Clarification on Brovana Reimbursement*, Apr. 26, 2007. www.aarc.org/headlines/07/04/brovana/ (last visited Jul. 26, 2010).
- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Spiller, L.D. and W.W. Wymer, *Physicians' Perceptions and Uses of Commercial Drug Information Sources: An Examination of Pharmaceutical Marketing to Physicians*, Health Marketing Quarterly 19.1, pp. 91–106. (2001).
- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Narayanan, S., et al., *Temporal Differences in the Role of Marketing Communication in New Product Categories*, Journal of Marketing Research 42 (Aug. 2005) pp. 278–290.
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- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Berndt, E.R., et al., *The roles of marketing, product quality and price competition in the growth and composition of the US antiulcer drug industry*, in The Economics of New Goods, ed. Timothy Bresnahan and Robert J. Gordon (Chicago: University of Chicago Press, 1997).
- Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Rosenthal, M.B., et al., *Demand Effects of Recent Changes in Prescription Drug Promotion*, Kaiser Family Foundation, Jun. 2003.
- Expert Report of Carlos Schuler, Oct. 23, 2009 (Dey).
- Expert Report of Carlos Schuler Exhibit 1: Curriculum Vitae for Carlos Schuler (Dey).
- Expert Report of Carlos Schuler Exhibit 2: List of Documents Considered (Dey).
- Expert Report of Carlos Schuler Exhibit 3: Brovana® labeling and Medication Guide.
- Expert Report of Carlos Schuler Exhibit 4: Perforomist® labeling and Medication Guide.
- Expert Report of Carlos Schuler Exhibit 5: Foradil® labeling.
- Expert Report of Carlos Schuler Exhibit 6: U.S. Patent No. 6,150,418 (provided as Document A93).

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- Expert Report of Carlos Schuler Exhibit 7: Dalby, R.; Spallek, M.; Vashaar, T., *A Review of the Development of Respimat® Soft Mist™ Inhaler*, International Journal of Pharmaceutics 283 (2004) 1–9.
- Expert Report of Carlos Schuler Exhibit 8: Respimat® promotional materials (located at <http://www.respimat.com/homepage.jsp>), last visited Jul. 15, 2010.
- Expert Report of Carlos Schuler Exhibit 9: Pari Nebulizer.
- Expert Report of Carlos Schuler Exhibit 10: Spiriva® User Guide.
- Expert Report of Carlos Schuler Exhibit 11: PCT Publication W091/14468.
- Expert Report of Carlos Schuler Exhibit 12: PCT Publication W097/12687.
- Expert Report of Carlos Schuler Exhibit 13: U.S. Patent No. 7,571,722.
- Expert Report of Carlos Schuler Exhibit 14: Zierenberg, et al., *Boehringer Ingelheim Nebulizer Binebo® A New Approach to Inhalation Therapy*, Respiratory Drug Delivery V, 1996 (p. 187–193).
- Expert Report of Carlos Schuler Exhibit 15: PCT Publication W097/39831.
- Expert Report of Carlos Schuler Exhibit 16: German Patent Publication DE 198 47 968.
- Expert Report of Carlos Schuler Exhibit 17: US Patent No. 6,481,435 (provided as Document A125).
- Expert Report of Carlos Schuler Exhibit 18: Spallek, M.W., et al., *Scale-Up And Production Challenges Of Bringing Respimat® Soft Mist™ Inhaler (SMI) To Market* Respiratory Drug Delivery IX, 2004 (p. 263–270).
- Expert Report of Carlos Schuler Exhibit 19: Clark et al., *Formulation of Proteins for Pulmonary Delivery*, Protein Formulation and Delivery Second Edition (Drugs and the Pharmaceutical Sciences), p. 219–253.
- Expert Report of Carlos Schuler Exhibit 20: Kunkel, G. et al., *Respimat® (a New Soft Mist Inhaler) Delivering Fenoterol plus Ipratropium Bromide Provides Equivalent Bronchodilation at Half the Cumulative Dose Compared with a Conventional Metered Dose Inhaler in Asthmatic Patients*, Respiration 2000;67:306–314.
- Expert Report of Carlos Schuler Exhibit 21: Ganderton, D., *Targeted delivery of inhaled drugs: current challenges and future goals*, J Aerosol Med., 12 (suppl. 1), pp. 3–8 (1999).
- Expert Report of Carlos Schuler Exhibit 22: Goldberg et al., *Improved delivery of fenoterol plus ipratropium bromide using Respimat® compared with a conventional metered dose inhaler*, Eur Respir J. 2001; 17: 225–232.
- Expert Report of Carlos Schuler Exhibit 23: Vincken et al., *Fenoterol Delivery by Respimat® Soft Mist Inhaler Versus CFC Metered Dose Inhaler: Cumulative Dose-Response Study in Asthma Patients*, Journal of Asthma, vol. 40, No. 6 pp. 721–730 (2003).
- Expert Report of Carlos Schuler Exhibit 24: Vincken et al., *Long-Term Efficacy and Safety of Ipratropium Bromide plus Fenoterol via Respimat® Soft Mist™ Inhaler (SMI) versus a Pressurized Metered-Dose-Inhaler in Asthma*, Clin. Drug. Invest. 2004;24 (1): 17–28.
- Expert Report of Carlos Schuler Exhibit 25: Hochrainer et al., *Comparison of the Aerosol Velocity and Spray Duration of Respimat® Soft Mist™ Inhaler and Pressurized Metered Dose Inhalers*, J. Aerosol Medicine 2005, vol. 18, No. 3, pp. 273–282.
- Opening Expert Report of Robert Williams III, Sep. 25, 2009.
- Opening Expert Report of Robert Williams III Exhibit 1: Curriculum Vitae for Robert Williams III.
- Opening Expert Report of Robert Williams III Exhibit 2: U.S. Patent No. 3,994,974 (provided as Document A23).
- Opening Expert Report of Robert Williams III Exhibit 3: U.S. Patent No. 6,040,344 (provided as Document A85).
- Opening Expert Report of Robert Williams III Exhibit 4: Byron, P.R., *Aerosol Formulation, Generation, and Delivery Using Nonmetered Systems*, Respiratory Drug Delivery, Ch. 6, pp. 143–165.
- Opening Expert Report of Robert Williams III Exhibit 5: “Sodium Hydroxide,” The Merck Index, 12th Ed., pp. 8772–8773 (1996).
- Opening Expert Report of Robert Williams III Exhibit 6: *Aerosols in Medicine: Principles, Diagnosis and Therapy*, (ed. by Moren, F., Dolovich, M.B., Newhouse, M.T. and Newman, S.P., Second, revised edition, pp. 340–350 1993).
- Opening Expert Report of Robert Williams III Exhibit 7: Stoklosa, M.J. et al., *Pharmaceutical Calculations*, 7th Ed., pp. 196–197 (1980).
- Opening Expert Report of Robert Williams III Exhibit 8: *Handbook of Pharmaceutical Excipients*, 3rd Ed., (ed. Kibbe, A.H.), “Citric Acid Monohydrate,” pp. 140–142 (2000).
- Opening Expert Report of Robert Williams III Exhibit 9: *Pharmaceutical Inhalation Aerosol Technology*, (ed. by Hickey, A.J.), 54: 166–167 (1992).
- Opening Expert Report of Robert Williams III Exhibit 10: Formoterol Fumarate Inhalation Solution 20 mcg/2mL Pharmaceutical Development Report (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 11: Formoterol Fumarate Inhalation Solution 20 mcg/2mL Analytical Procedures (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 13: GAO Arformoterol Tartrate and Murakami Fumarate Tables.
- Opening Expert Report of Robert Williams III Exhibit 14: GAO Arformoterol Tartrate and Murakami Fumarate Tables.
- Opening Expert Report of Robert Williams III Exhibit 15: Study Report Dey Formoterol Fumarate vs. U.S. Patent 6,150,418 (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 16: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 17: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 18: Stability Data of Formoterol Low Drug Concentration (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 19: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 20: Effect of pH on Degradation of Formoterol (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 21: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 22: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].

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Opening Expert Report of Robert Williams III Exhibit 23: Data for Formoterol High Dose (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Robert Williams III Exhibit 24: Stability Study for Formoterol Fumarate Inhalation Solution 20 mcg/2mL (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Robert Williams III Exhibit 37: Formulation Comparison (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Robert Williams III Exhibit 38: Formulation Comparison (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Robert Williams III Exhibit 39: [Sepracor Confidential—Copy Not Available].

Opening Expert Report of Robert Williams III Exhibit 40: Declaration of P. Banerjee dated Sep. 24, 2004 submitted in U.S. Appl. 09/887,496 (Dey).

Opening Expert Report of Robert Williams III Exhibit 41: Table Supporting Declaration of P. Banerjee dated Sep. 24, 2004 submitted in U.S. Appl. No. 09/887,496 (Dey).

Opening Expert Report of Robert Williams III Exhibit 42: Listing of Documents Reviewed.

Opening Expert Report of Robert Williams III Exhibit 43: Lab Notebook [Dey Confidential—Filed Under Seal].

Opening Expert Report of Robert Williams III Exhibit 44: Lab Notebook [Dey Confidential—Filed Under Seal].

Opening Expert Report of Robert Williams III Exhibit 45: Method Qualification Results (Murakami and Gao) (Dey).

Expert Report of Robert Williams III, Nov. 20, 2009 [Dey Confidential—Filed Under Seal] [Sepracor Confidential—Redacted].

Reply Expert Report of Robert Williams III Exhibit 46: Method Validation Report for HPLC Assay of Formoterol Fumarate and its Related Substances in Formoterol Fumarate Inhalation Solution, 20 mcg/2mL (ATM-716-13) (Sepracor) [Dey Confidential—Filed Under Seal].

Reply Expert Report of Robert Williams III Exhibit 50: Study table (Sepracor) [Dey Confidential—Filed Under Seal].

Reply Expert Report of Robert Williams III Exhibit 51: Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL (Sepracor) [Dey Confidential—Filed Under Seal].

Reply Expert Report of Robert Williams III Exhibit 52: U.S. Patent No. 6,150,418 (provided as Document A93).

Reply Expert Report of Robert Williams III Exhibit 55: Listing of Additional Documents Reviewed.

Akapo Deposition Transcript, Dec. 10, 2008 (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 51: Personal Action Form (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 52: Employee Self Appraisal (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 53: U.S. Appl. No. 60/284,606.

Akapo Deposition Exhibit 54: U.S. Patent No. 6,667,344 w/Partial File History.

Akapo Deposition Exhibit 55: U.S. Patent No. 6,814,953 w/Partial File History.

Akapo Deposition Exhibit 56: U.S. Patent No. 7,348,362 w/Partial File History.

Akapo Deposition Exhibit 57: United States Code, Title 18, §§ 1001 to 1200.

Akapo Deposition Exhibit 58: S. Akapo Award for the Perforomist Patents (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 59: A Comparative Stability Study Of Formoterol In Active Substance Concentrate (US Patent #6,150,418) and Dey's Formoterol Fumarate Inhalation Solutions (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 60: U.S. Patent No. 6,150,418 (provided as Document A93).

Akapo Deposition Exhibit 61: Summary of Formoterol work done by M. Joyce (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 62: Summary of Stability Study for Formoterol Fumarate Inhalation Placebo (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 63: A stability-indicating HPLC assay method for formoterol and its related substances in formoterol fumarate dihydrate drug substance (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 64: Heat Degradation Study of Formoterol Inhalation Solution (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 65: Oral Inhalation PDT Meeting Minutes From Apr. 16, 2003 (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 66: Akapo, S., et al., *Validation of a RP-HPLC method for the assay of formoterol and its related substances in formoterol fumarate dihydrate drug substance*. J. Pharm. Biomed. Anal. 33 (2003) 935–945.

Akapo Deposition Exhibit 67: Shelf Life Projection For Formoterol Fumarate Inhalation Solutions (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 68: E-mail (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 69: E-mail (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 70: E-mail (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 71: Formoterol PDT Meeting Minutes From Jan. 12, 2005 (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 72: Analytical Procedures (Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL) (Dey) [Dey Confidential—Filed Under Seal].

Akapo Deposition Exhibit 73: Method Validation Report for HPLC Assay of Formoterol Fumarate and its Related Substances in Formoterol Fumarate Inhalation Solution, 20 mcg/2mL (ATM-716-13) (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Transcript, Feb. 13, 2009 (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Exhibit 118: Banerjee et al., *Studies on the Effects of Some Additives on the Stability of Injectable Formulations of Diazepam*, Indian Drugs 29 (8), 361–364 (May 1992).

First Banerjee Deposition Exhibit 119: Letter from Banerjee to Patent Counsel with references (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Exhibit 119[A]: Faulds, D., et al., *Formoterol A Review of its Pharmacological Properties and Therapeutic Potential in Reversible Obstructive Airways Disease*. Drugs 42 (1) pp. 115–137 1991 Use Document on Desksite—Not Printed From E-Room.

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- First Banerjee Deposition Exhibit 119[B]: Maesen, F.P.V., et al., *Formoterol Suspension Aerosol Comparison with Formoterol Solution Aerosol for 12 Weeks in Asthmatic Patients*. Chest 102:1544-1549 (1992) (provided as Document C45).
- First Banerjee Deposition Exhibit 119[C]: U.S. Patent No. 6,004,537 (provided as Document A82).
- First Banerjee Deposition Exhibit 119[D]: Anderson, G.P., *Formoterol: Pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective β_2 -adrenoceptor agonist bronchodilator*. Life Sciences, vol. 52, No. 26 pp. 2145-2160 (1993).
- First Banerjee Deposition Exhibit 119[E]: Bartow, R.A., et al., *Formoterol An Update of its Pharmacological Properties and Therapeutic Efficacy in the Management of Asthma Drugs*, 55 (2) pp. 303-322 (Feb. 1998). (provided as Document C2).
- First Banerjee Deposition Exhibit 119[F]: PCT Publication WO 99/36095 (provided as Document B34).
- First Banerjee Deposition Exhibit 119[G]: PCT Publication WO 99/00134 (provided as Document B30).
- First Banerjee Deposition Exhibit 120: File History U.S. Patent No. 6,667,344.
- First Banerjee Deposition Exhibit 121: Dey Product Development Monthly Report—Apr. 1999 (Dey) [Dey Confidential—Filed Under Seal].
- First Banerjee Deposition Exhibit 122: Dey Product Development Monthly Report—Jun. 1999 (Dey) [Dey Confidential—Filed Under Seal].
- First Banerjee Deposition Exhibit 123: Oral Inhalation PDT Meeting Minutes—Oct. 1999 (Dey) [Dey Confidential—Filed Under Seal].
- First Banerjee Deposition Exhibit 124: Oral Inhalation PDT Meeting Minutes—Apr. 2000 (Dey) [Dey Confidential—Filed Under Seal].
- First Banerjee Deposition Exhibit 125: Formoterol Fumarate Formulation Activities (Dey) [Dey Confidential—Filed Under Seal].
- First Banerjee Deposition Exhibit 126: Dey Formulation Composition (Dey) [Dey Confidential—Filed Under Seal].
- First Banerjee Deposition Exhibit 127: E-mail patent reminder (Dey) [Dey Confidential—Filed Under Seal].
- First Banerjee Deposition Exhibit 128: U.S. Patent No. 7,462,645 (provided as Document A137).
- First Banerjee Deposition Exhibit 129: U.S. Patent No. 7,473,710 (provided as Document A139).
- First Banerjee Deposition Exhibit 130: U.S. Patent No. 7,465,756 (provided as Document A138).
- Second Banerjee Deposition Transcript, Sep. 15, 2009 (Dey) [Dey Confidential—Filed Under Seal].
- Second Banerjee Deposition Exhibit 180: Personnel Action Form (Dey) [Dey Confidential—Filed Under Seal].
- Second Banerjee Deposition Exhibit 181: Correspondence between Dey and Patent Counsel (Dey) [Dey Confidential—Filed Under Seal].
- Second Banerjee Deposition Exhibit 182: Declaration of P. Banerjee dated Sep. 24, 2004 submitted in U.S. Appl. No. 09/887,496.
- Second Banerjee Deposition Exhibit 183: Lab Notebook (Dey) [Dey Confidential—Filed Under Seal].
- Second Banerjee Deposition Exhibit 184: Formoterol Fumarate Nebulization U.D.—For the treatment of COPD (Dey) [Dey Confidential—Filed Under Seal].
- Second Banerjee Deposition Exhibit 185: Citations from Biological Abstracts (Dey) [Dey Confidential—Filed Under Seal].
- Second Banerjee Deposition Exhibit 186: Converted concentrations from Formoterol fumarate to Formoterol free base. (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Transcript, Feb. 5, 2009 (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 99: Dey Scientific Affairs Track record Jan. 2004–Aug. 2007 (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 100: Dey to Center for Drug Research—Change of Correspondence (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 101: Minutes from Apr. 23, 2004 NPC Meeting (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 102: Application To Market A New Drug, Biologic, Or An Antibiotic Drug For Human Use (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 103: E-mail transmitting Formoterol Patent Opinion (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 104: Letter to FDA Formoterol Fumarate Inhalation Solution, 20 mcg/mL—Petition To Correct Patent Information (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 105: Letter to FDA Perforomist™ (formoterol fumarate) Inhalation Solution 20 mcg/2 mL Submission of Patent Information (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 106: PDT Update Sep. 23, 2004 (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 107: Formoterol PDT Meeting Minutes From Oct. 13, 2004 (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 108: Chronology Regulatory & Clinical Activities Formoterol Fumarate (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 109: Formoterol—Quality 5% desformyl degradant (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 110: EOP2 FDA Meeting Action Plan (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 111: Memorandum of Meeting Minutes with FDA on May 13, 2003 (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 112: Formoterol PDT Meeting Minutes From Sep. 8, 2004 (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 113: Formoterol Unit Dose for COPD (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 114: Formoterol Pls (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 115: Oral Inhalation PDT Meeting Minutes From Jul. 10, 2002 (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 116: Oral Inhalation PDT Meeting Minutes From Nov. 13, 2002 (Dey) [Dey Confidential—Filed Under Seal].
- Carpenter Deposition Exhibit 117: Letter from Dey to FDA Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL Minor Amendment—Patent Certification Amendment (Dey) [Dey Confidential—Filed Under Seal].

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First Chaudry Deposition Transcript, Jun. 30, 2009 (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 142: Deposition of I. Chaudry in *Dey v. Ivax Pharmaceuticals* in the United States District Court for the Central District of California, Civil Action No. SACV 04-00079 (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 143: Letter between litigation counsel regarding discovery (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 144: Correspondence between Dey and Patent Counsel (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 145: Stability of Formoterol Fumarate in Purified Water (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 146: Dey Invention Award Plan (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 147: Dey Inventor Incentive Award Calculations (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 148: Formoterol Overview Stage II (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Transcript, Jul. 1, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 126A: Formulation Composition (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 149: Oral Inhalation PDT Meeting Minutes From Oct. 2000 (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 150: Stability and Expiration Dating of Formoterol (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 151: Letter regarding Formoterol U.D. (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 152: Merck Innovation Award (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 153: Sepracor's Rule 30(b)(6) Notice of Deposition in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 154: Sepracor's Third Rule 30(b)(6) Notice to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 155: I. Chaudry Employee Profile (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 156: Scientific Affairs MBO 2004 (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 157: Scientific Affairs MBO 2005 (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 158: Estimate of Nebulization Market Size (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 159: Formoterol Fumarate IS Solution pH (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Transcript, Jan. 30, 2009 (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 74: Dey Portfolio Presentation (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 75: E-mail regarding Formoterol Patent (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 76: Minutes from the NPC Meeting Day 2005 (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 77: Publication and Abstract Plan (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 78: Minutes from the Medical Advisors Meeting, May 2005 (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 79: 2004 R&D Plan and Project Prioritization (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 80: Presentation of Professor Scheuble—Business Development Update (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 81: Perforomist Launch Delay Memo (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 82: Formoterol U.D. Memo (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 83: Timing in 20% Reduction in Sales Force (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 84: Dey Award Plan for Inventions (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 85: E-mail regarding Sepracor (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 86: Presentation of Dey Award for the Perforomist Patents (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 87: E-mail regarding out licensing (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 88: Co-promotion agreement with Dey and Critical Therapeutics (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 89: E-mail regarding 4-year plan impacts (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 90: Revised Plaintiff's Privileged Log (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 91: Senior Team Meeting Minutes (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 92: E-mail for "formoterol disaster" (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 93: Dey Net Sales Projection (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 94: Pipeline Activity Summary (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 95: Antwort Respiratory Strategy (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 96: Net Sales Report (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 97: Perforomist Net Sales (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 98: North America Mgt Presentation—Pipeline Page (Dey) [Dey Confidential—Filed Under Seal].

Second Engle Deposition Transcript, Sep. 16, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Transcript, Aug. 13, 2009 (Dey) [Dey Confidential—Filed Under Seal].

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Glascott Deposition Exhibit VG1: Sepracor's Second Rule 30(b)(6) Notice to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, Mar. 21, 2007 [Pam Marrs 1] [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG2: Press Release Mylan's Dey L.P. Announces Establishment of 'J-Code' for Perforomist™ Inhalation Solution.

Glascott Deposition Exhibit VG3: Draft Updated Medical Policy for Medicare and Medicaid (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG4: Bates Ranges (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG5: Letter to TrustSolutions with additional information regarding Perforomist™ (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG6: Border, M, *Treatment Algorithms for Chronic Obstructive Pulmonary Disease*, Dec. 2006, Decision Resources, 2006 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG7: Monie, D., *Chronic Obstructive Pulmonary Disease Treatment & Reimbursement—Findings from a U.S. Survey of PCPs, Pulmonologists, and Managed Care Pharmacy Directors*, Decision Resources, Nov. 2006 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG8: Review of Dey Sales Projections (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG9: Situational Analysis of Chronic Obstructive Pulmonary Disease (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG10: US Formoterol Market Overview, Mar. 2002 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG11: Unit Dose Opportunity Assessment (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG12: Marketing Definition Memo (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG13: New Market Definitions (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG14: Price per day Comparison on WAC (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG15: Formoterol Launch Forecast (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG16: Perforomist™ Projections (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG17: Perforomist™ Retail Price Summary (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG18: E-mail regarding Perforomist™ Launch Offer Recco (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG19: Pricing Recommendation for Perforomist™ Inhalation Solution (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG20: Branded Pipeline Forecast by Indication and Segment (Dey) [Dey Confidential—Filed Under Seal] [Pam Marrs 30].

Glascott Deposition Exhibit VG21: E-mail regarding discussion with Bankers (Dey) [Dey Confidential—Filed Under Seal] [Pam Marrs 27].

Glascott Deposition Exhibit VG22: Formoterol Lost Profits (Dey) [Dey Confidential—Filed Under Seal] [Pam Marrs 23].

Glascott Deposition Exhibit VG23: Optimal Bronchodilation in COPD: Making a Long Story Short (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG24: E-mail FFIS Field Strategy (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG25: E-mail Retention and Maintenance C27100 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG26: E-mail DuoNeb vs Brovana Sales aid (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG27: Formoterol Competitive Workshop (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG28: Brovana War Games Summary (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG29: Dey Formoterol Forecast Compared to Arformoterol forecast (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG30: Perforomist Message to Internal and External Customers (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG31: E-mail on Back-orders- (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG32: Marketing Department Org Chart (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG33: Formoterol Launch Plan Update (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG34: Formoterol Transition Plan (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG35: Formoterol Launch Commercialization Team (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG36: Formoterol Update (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG37: FFIS Launch Commercialization Meeting Jan. 10, 2007 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG38: FFIS Launch Commercialization Meeting Feb. 1, 2007 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG39: Perforomist™ National Sales Plan (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG40: 2008 Perforomist™ Inhalation Solution Launch Marketing Plan (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG41: 2008 Perforomist™ Inhalation Solution Launch Marketing Plan (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Transcript, Aug. 11, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX165: Updated Summary of Formoterol PAI Preparation Meetings (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX166: Stability Data for Formoterol Fumarate Inhalation Solution, 20 mcg/2mL (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX167: Finished Product Methods Requiring Transfer Qualifications (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX168: HPLC Assay of Formoterol Fumarate and its Related Substances in Formoterol Fumarate Inhalation Solution (20 mcg/2mL and 20 mcg/0.5 mL) (Dey) [Dey Confidential—Filed Under Seal].

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Gupta Deposition Exhibit DX169: Stability Study Protocol for Dey's Performist™ (Formoterol Fumarate) Inhalation Solution Against Sepracor's Brovana™ (Arformoterol Tartrate) Inhalation Solution (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX170: Analytical Development Test Request for Brovana™ (Arformoterol Tartrate) Inhalation Solution 15 mcg/2 mL (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX171: Analytical Development Test Request for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX172: Analytical Development Test Request for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL—1 month @ 25±2 ° C./60±5 %RH (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX173: Analytical Development Test Request for Brovana™ (Arformoterol Tartrate) Inhalation Solution, 15 mcg/2 mL—1 month @ 25±2 ° C./60±5 %RH (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX174: Analytical Development Test Request for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL—2 month @ 25±2 ° C./60±5 %RH (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX175: Analytical Development Test Request for Brovana™ (Arformoterol Tartrate) Inhalation Solution, 15 mcg/2 mL—2 month @ 25±2 ° C. 60±5 %RH (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX176: Lab Notebook (Dey).

Gupta Deposition Exhibit DX177: Lab Notebook (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX178: Akapo, et al. *Evaluation of Interconversion of (RR)- and (SS)-Enantiomers in Performist™ (Formoterol Fumarate) and Brovana™ (Arformoterol Tartrate) Inhalation Solutions* (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Transcript, Sep. 5, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX1: Serpacor's Rule 30(b)(6) Notice of Deposition of Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX2: Dey's Initial Disclosures in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX3: Serpacor's First Set of Requests for the Production of Documents to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07 cv 2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX4: Serpacor's Second Set of Requests for the Production of Documents to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX5: Serpacor's Third Set of Requests for the Production of Documents to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX6: Subpoena of Heller Ehrman in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX7: Revised Agreement for Electronic Discovery in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Kling Deposition Transcript, Aug. 20, 2009 (No Exhibits) (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Transcript, Sep. 11, 2008 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX34: Orange Book Detail Search for Formoterol Fumarate.

Laskar Deposition Exhibit DX35: NDA Description and Composition of the Drug Product (Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX36: Oral Inhalation PDT Meeting Minutes From Jul. 9, 2003 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX37: Oral Inhalation PDT Meeting Minutes From Feb. 11, 2004 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX38: Pharmaceutical Development MBOs (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX39: Date of the formulation of the 10 mcg/mL composition. (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX40: Ayres, J, et al., *Student Experiments In Pharmaceuticals I.V. Additives, Chemical Incompatibilities, Kinetics, And The Arrhenius Equation*. American Journal of Pharmaceutical Education, Student Experiments in Pharmaceuticals, pp. 58–68.

Laskar Deposition Exhibit DX41: Laskar, P., et al., *Degradation of Carmustine in Aqueous Media*. Journal of Pharmaceutical Sciences, vol. 66, No. 8, pp. 1073–1076, Aug. 1977.

Laskar Deposition Exhibit DX42: U.S. Patent Publication 2005/0009836.

Laskar Deposition Exhibit DX43: PCT Publication WO 93/20796.

Laskar Deposition Exhibit DX44: Pharmaceutical Development Report Formoterol Fumarate Inhalation Solution 20 mcg/2 mL (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX45: U.S. Patent No. 6,161,536 (provided as Document A95).

Laskar Deposition Exhibit DX46: Formoterol PDT Meeting Minutes From May 11, 2005 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX47: Draft Minutes from the NPC Meeting held Jul. 19, 2005 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX48: Pharmaceutical Development MBOs 2005 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX49: Dey Innovation Note (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX50: Edits/Questions for Pharm/Tox Sections (Dey) [Dey Confidential—Filed Under Seal].

Lee Deposition Transcript, Jul. 14, 2009 (Dey) [Dey Confidential—Filed Under Seal].

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Lee Deposition Exhibit DX160: Ex Parte Reexamination Request for U.S. Patent No. 6,667,344 (Copy not submitted, see Reexamination No. 90/010,488).

Lee Deposition Exhibit DX161: Ex Parte Reexamination Request for U.S. Patent No. 6,814,953 (Copy not submitted, see Reexamination No. 90/010,489).

Lee Deposition Exhibit DX162: Privilege Log (Dey) [Dey Confidential—Filed Under Seal].

Lee Deposition Exhibit DX163: Order Granting Ex Parte Reexamination Request for U.S. Patent No. 6,667,344 (Copy not submitted, see Reexamination No. 90/010,488).

Lee Deposition Exhibit DX164: Order Granting Ex Parte Reexamination Request for U.S. Patent No. 6,814,953 (Copy not submitted, see Reexamination No. 90/010,489).

First Marrs Deposition Transcript, Aug. 12, 2009 (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM1: Sepracor's Second Rule 30(b)(6) Notice to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 [VG1] (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM2: Dey's Supplement Objections And Responses To Sepracor's First Set Of Interrogatories To Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM3: Dey Net Sales Perforomist (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM4: Dey Perforomist 2008 Actual (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM5: Dey Perforomist 2009 Actual (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM6: 2007 Key Indicator Graphs (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM7: Formoterol UD NDA Communication (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM8: Investment Committee Meeting (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM9: Capital Request for Molds (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM10: E-mail regarding vial design (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM11: Perforomist Inventory on Hand (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM12: E-mail on Back-orders (Dey) [Dey Confidential—Filed Under Seal] [VG31].

First Marrs Deposition Exhibit PM13: Message to the Senior Team (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM14: Summary of Net Sales Changes 2007 & 2008 (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM15: Impact on Formoterol (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM16: Various Projections in 2015 Scenarios (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM17: Dey Amendment No. 3 to Form S-1 Registration Statement.

First Marrs Deposition Exhibit PM18: E-mail regarding Formoterol Forward (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM19: Orange Book Detail Search for Arbuterol Sulfate.

First Marrs Deposition Exhibit PM20: U.S. Patent No. 6,632,842 (provided as Document A128).

First Marrs Deposition Exhibit PM21: IIP Analysis (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM22: Formoterol Forecast based on Launch Dates (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM23: Formoterol Lost Profits (Dey) [Dey Confidential—Filed Under Seal] [VG22].

First Marrs Deposition Exhibit PM24: Formoterol Increased sales from early launch of 2 ml vs lost LV sales (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM25: Formoterol Oct. 2007 Launch Sales (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM26: Formoterol Low Volume Discontinuance (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM27: E-mail regarding discussion with Bankers (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM28: E-mail regarding conversation with bankers, extended (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM29: E-mail regarding "beta-agonist" (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM30: Branded Pipeline Forecast by Indication and Segment (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM31: Branded Budgeted Development Projects (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM32: Dey Sales Revised 4 Year Plan (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM33: Dey P&L Summary (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM34: Formoterol P&L to 2011 (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM35: Market Share Forecast (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM36: Patent Share Chart (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM37: Dey Sales by Product (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM38: Dey Sales & Margin Before CAMS (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM39: Dey 2008 Budget (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM40: Dey 2007 Strategic Plan (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Transcript, Sep. 24, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM41: Dey Sales All Products (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM42: 2008 Product Line P&L Analysis vol. 1 Actual (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM43: 2008 Product Line P&L Analysis vol. 2 Actual (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM44: Dey Gross to Net Sales (Dey) [Dey Confidential—Filed Under Seal].

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Second Marrs Deposition Exhibit PM45: Fixed Assets Acquired Specifically for Performist (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM46: Performist Rebate for Neighborhood Health Plan (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM47: Performist Rebate for Beyond Rx (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM48: Contract Renewal for Virtua Health (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM49: FFDIS Developing a US Pricing and Market Access Strategy (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM50: Performist™ Miscellaneous Correspondence (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM51: New Market Definitions (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM52: E-mail on FFIS Pre-appr Field Strategy (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM53: Branded Pipeline Forecasts by Indication and Segment (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Transcript, Sep. 23, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Exhibit 131: U.S. Patent No. 7,541,385 (provided as Document A140).

Mercanti Deposition Exhibit 132: Declaration of Michael N. Mercanti, Esq. in Support of Dey's Opposition to Sepracor's Motion for Leave to File an Amended Answer and Counterclaims in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Exhibit 133: Dey's Supplemental Objections And Responses To Sepracor's First Set Of Interrogatories To Dey (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Exhibit 134: U.S. Patent No. 7,462,645 and partial File History.

Mercanti Deposition Exhibit 135: U.S. Patent No. 7,473,710 and partial File History.

Mercanti Deposition Exhibit 136: U.S. Patent No. 7,465,756 and partial File History.

Mercanti Deposition Exhibit 137: U.S. Patent No. 7,541,385 and partial File History.

Mercanti Deposition Exhibit 138: Partial File History U.S. Appl. No. 09/887,496.

Mercanti Deposition Exhibit 139: Final Office Action mailed May 26, 2009 in U.S. Appl. No. 10/145,978.

Mercanti Deposition Exhibit 140: Privileged Log (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Exhibit 141: Sepracor's Answer And Counterclaims To Dey's Second Supplemental Complaint in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Transcript, Sep. 9, 2008 (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX08: U.S. Patent No. 6,677,344 (provided as Document A129).

Pham Deposition Exhibit DX09: U.S. Patent No. 6,814,953 (provided as Document A133).

Pham Deposition Exhibit DX10: U.S. Patent No. 7,348,362 (provided as Document A136).

Pham Deposition Exhibit DX11: Project Assignment For Unit Dose Scientists (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX12: Declaration and Power of Attorney for U.S. Appl. No. 09/887,281.

Pham Deposition Exhibit DX13: Formoterol Fumarate Inhalation Solution 20 mcg/2 mL Original NDA (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX14: Formoterol Fumarate Inhalation Solution Clinical Batches (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX15: Formulation Selection Memo (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX16: Pharmaceutical Development MBOs (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX17: Formoterol Solubility and pH Stability Profile (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX18: U.S. Patent No. 6,040,344 (provided as Document A85).

Pham Deposition Exhibit DX19: Petitions to Correct Inventorship in Patent No. 6,667,344.

Pham Deposition Exhibit DX20: Petitions to Correct Inventorship in Patent No. 6,814,953.

Pham Deposition Exhibit DX21: Application for Patent No. 7,348,362.

Pham Deposition Exhibit DX22: Petitions to Correct Inventorship in U.S. Appl. No. 10/887,785.

Pham Deposition Exhibit DX23: Formoterol Updates (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX24: Maesen, FP., et al., *Formoterol suspension aerosol. Comparison with formoterol solution aerosol for 12 weeks in asthmatic patients*. Chest 102:1544-1549 (1992) (provided as Document C45).

Pham Deposition Exhibit DX25: Merck Innovation Award (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX26: Preliminary Stability Assessment Of Formoterol Fumarate In Aqueous Solution (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX27: Formulation Development of Formoterol Inhalation Unit Dose (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX28: Summary of Formoterol Unit Dose Formulation Development (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX29: Formulation Selection Justification Report (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX30: Formoterol Unit Dose—Timeline and Key Milestones (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX31: Letter to D. Rieger (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX32: U.S. Patent No. 3,994,974 (provided as Document A23).

Pham Deposition Exhibit DX33: Response to Final Office Action, mailed Apr. 22, 2003 in U.S. Appl. No. 09/887,281.

Rieger Deposition Transcript, Aug. 19, 2009 (Dey) [Dey Confidential—Filed Under Seal].

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- Rieger Deposition Exhibit DX179: Feb. 25, 2003 Fax Transmission from Partha S. Banerjee to Dale L. Rieger, Ph.D.; Composition of Formoterol Clinical Formulation (Dey) [Dey Confidential—Filed Under Seal].
- A Comparative Stability Study Of Formoterol In Active Substance Concentrate (US Patent #6,150,418 [to Hochrainer et al.]) and Dey's Formoterol Fumarate Inhalation Solutions Oct. 10, 2005.
- Stenesh, J., *Dictionary of Biochemistry and Molecular Biology* (2d ed. 1989), p. 364.
- Sterns, R.H. et al., *Salt and water: read the package insert*, Q. J. Med. (2003), 96:549–552.
- Bates, R. et al., *Standards for pH Measurements in Isotonic Saline Media of Ionic Strength I=0.16*, Analytical Chemistry (vol. 50, No. 9, Aug. 1978), 1295–1300.
- Roy, R. et al., *Buffer Standards for the Physiological pH of Zwitterionic Compounds, MOBS and TABS from 5 to 55 °C*, J. Solution Chemistry (vol. 33, No. 10, Oct. 2004), pp. 1199–1211.
- Docket Sheet dated Apr. 5, 2011 in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-02353-JGK-RLE, Mar. 21, 2007.
- Docket Sheet dated Apr. 5, 2011 in *Dey v. Teva* in the United States District Court for the Northern District of West Virginia, Civil Action No. 1:09-cv-00087-IMK, Jun. 23, 2009.
- Defendant's Supplemental Responses to Plaintiffs' First Set of Interrogatories dated Jan. 21, 2011 in *Dey v. Teva* in United States District Court for the Northern District of West Virginia, Civil Action No. 1:09-cv-00087-IMK, Jun. 23, 2009 (Teva) [Dey Confidential—Filed Under Seal] [Teva Confidential—Redacted].
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit dated Oct. 1, 2010 in *Dey v. Teva* in United States District Court for the Northern District of West Virginia, Civil Action No. 1:09-cv-00087-IMK, Jun. 23, 2009.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit A: U.S. Patent No. 6,667,344.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit B: U.S. Patent No. 6,814,953.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit C: U.S. Patent No. 7,348,362.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit D: U.S. Patent No. 7,462,645.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit E (6 parts): Excerpts from the Reexamination Files of the '344 Patent (Reexamination No. 90/010,488) and the '953 Patent (Reexamination No. 90/010,489).
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit F (4 parts): Excerpts from the File History of U.S. Appl. No. 09/887,281.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit G (8 parts): Excerpts from the File History of U.S. Appl. No. 10/138,866.
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**EX PARTE
REEXAMINATION CERTIFICATE
ISSUED UNDER 35 U.S.C. 307**

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claim 61 is cancelled.

Claims 1, 5, 10, 22-26, and 39-43 are determined to be patentable as amended.

Claims 2-4, 6-9, 11-21, 27-38, 48, 62, 65 and 68-74, dependent on an amended claim, are determined to be patentable.

New claims 89-120 are added and determined to be patentable.

Claims 44-47, 49-60, 63, 64, 66, 67 and 75-88 were not reexamined.

1. A pharmaceutical composition, comprising formoterol, or a derivative thereof, in a pharmacologically suitable [fluid] aqueous solution, wherein the composition is stable during long term storage, [the fluid comprises water, and] the composition is formulated at a concentration effect for bronchodilation by nebulization, and the composition is suitable for direct administration to a subject in need thereof, without propellant and without dilution of the composition prior to administration.

5. The pharmaceutical composition of claim 1, wherein the pharmacologically suitable [fluid] aqueous solution comprises a polar solvent.

10. The pharmaceutical composition of claim 1, wherein the pharmacologically suitable [fluid] aqueous solution comprises a buffer.

22. The pharmaceutical composition of claim 1, wherein the formoterol free base concentration is about 5 µg/mL to about [2 mg/mL] 50 µg/mL.

23. The pharmaceutical composition of claim 22, wherein the formoterol free base concentration is about [10] 5 µg/mL to about [1 mg/mL] 10 µg/mL.

24. The pharmaceutical composition of claim [23] 22, wherein the formoterol free base concentration is about [50] 10 µg/mL to about [200 mg/mL] 50 µg/mL.

25. The pharmaceutical composition of claim [24] 1, wherein the formoterol free base concentration is about 59 µg/mL.

26. The pharmaceutical composition of claim [24] 1, wherein the formoterol free base concentration is about 118 µg/mL.

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39. The pharmaceutical composition of claim 27, wherein the formoterol free base concentration is about 5 µg/mL to about [2 mg/mL] 50 µg/mL.

40. The pharmaceutical composition of claim 39, wherein the formoterol free base concentration is about [10] 5 µg/mL to about [1 mg/mL] 10 µg/mL.

41. The pharmaceutical composition of claim [40] 39, wherein the formoterol free base concentration is about [50] 10 µg/mL to about [200] 50 µg/mL.

42. The pharmaceutical composition of claim [41] 27, wherein the formoterol free base concentration is about 59 µg/mL.

43. The pharmaceutical composition of claim [41] 27, wherein the formoterol free base concentration is about 118 µg/mL.

89. A pharmaceutical composition comprising a single unit dosage form, the dosage form comprising a single use container, the contents of the container comprising about 2 mL of an aqueous solution comprising formoterol, a pharmaceutically acceptable salt thereof, or hydrate of said formoterol or salt, wherein the concentration of said formoterol, salt, or hydrate is equivalent to about 5 µg/mL to about 50 µg/mL of formoterol free base in the solution, and the composition is suitable for direct administration by nebulization without dilution for bronchodilation to a subject in need thereof, and is stable during long term storage.

90. A composition according to claim 89, wherein the concentration of the formoterol, salt or hydrate is equivalent to about 5 µg/mL to about 10 µg/mL of formoterol free base in the solution.

91. A composition according to claim 89, wherein the concentration of the formoterol, salt or hydrate is equivalent to about 10 µg/mL to about 50 µg/mL of formoterol free base in the solution.

92. A pharmaceutical composition according to claim 89, wherein the salt is a tartrate.

93. A pharmaceutical composition according to claim 89, wherein the salt is a fumarate.

94. A pharmaceutical composition according to claim 89, wherein the nebulization is conducted in a jet nebulizer.

95. A pharmaceutical composition according to claim 89, wherein the subject is human.

96. A pharmaceutical composition as defined in claim 89, wherein the nebulization is conducted in an ultrasonic nebulizer.

97. A pharmaceutical composition as defined in claim 89, wherein the nebulization is conducted in an electromagnetic nebulizer.

98. A pharmaceutical composition according to claim 89 wherein the aqueous solution comprises a saline solution.

99. A pharmaceutical composition according to claim 98, wherein the saline solution is isotonic.

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100. A pharmaceutical composition according to claim 89, wherein the solution further comprises a citrate buffer.

101. A pharmaceutical composition according to claim 100, wherein the citrate buffer comprises sodium citrate.

102. A pharmaceutical composition according to claim 100, wherein the citrate buffer comprises citric acid and sodium citrate.

103. A pharmaceutical composition according to claim 89, wherein the dosage form comprises an aqueous solution that is sterile.

104. A pharmaceutical composition according to claim 89, wherein the formoterol, salt or hydrate is provided as a mixture of enantiomers or stereoisomers of formoterol, or a salt or a hydrate thereof.

105. A pharmaceutical composition according to claim 89, wherein the formoterol, salt or hydrate is provided substantially as a single enantiomer or stereoisomer of formoterol, or a salt or a hydrate thereof.

106. A pharmaceutical composition according to claim 105, wherein the formoterol, salt, or hydrate provided substantially as a single enantiomer or stereoisomer optically pure.

107. A pharmaceutical composition according to claim 105, wherein the formoterol, salt, or hydrate consists of the free base, a salt or a hydrate of the enantiomer or stereoisomer

2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethylamino) ethyl) formanilide.

108. A pharmaceutical composition according to claim 106, wherein the formoterol, salt, or hydrate consists of the free base, a salt or a hydrate of the enantiomer or stereoisomer

2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethylamino) ethyl) formanilide.

109. A pharmaceutical composition according to claim 108, wherein the formoterol, salt, or hydrate consists of tartrate salt of the enantiomer or stereoisomer

2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethylamino) ethyl) formanilide.

110. A pharmaceutical composition according to claim 108, wherein the formoterol, salt, or hydrate consists of a fumarate salt of the enantiomer or stereoisomer

2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethylamino) ethyl) formanilide.

111. A pharmaceutical composition according to claim 105, wherein the formoterol, salt or hydrate consists of a formoterol tartrate or a formoterol fumarate.

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112. A pharmaceutical composition according to claim 111, wherein the formoterol, salt or hydrate consists of a formoterol fumarate dihydrate.

113. A pharmaceutical composition according to claim 111, wherein the formoterol, salt or hydrate consists of a formoterol tartrate.

114. A pharmaceutical composition comprising a single unit dosage form, the dosage form comprising a single use container, the contents of the container comprising about 2 mL of a sterile isotonic saline solution comprising a pharmaceutically acceptable salt of formoterol or a hydrate thereof and a citrate buffer, wherein the concentration of the formoterol salt is equivalent to about 5-50 µg formoterol free base per mL of solution, the dosage form is suitable for long term storage of the solution, and the solution does not require dilution before the administration by nebulization of a therapeutically effective amount for bronchodilation of the formoterol salt or hydrate to a human subject in need thereof.

115. A pharmaceutical composition according to claim 114, wherein the salt is a formoterol fumarate or a formoterol tartrate.

116. A pharmaceutical composition according to claim 115, wherein the salt is a formoterol fumarate dihydrate.

117. A pharmaceutical composition according to claim 115, wherein the salt is a formoterol tartrate.

118. A pharmaceutical composition comprising a single unit dosage form, the dosage form comprising a single use container, the contents of the container comprising about 2 mL of a sterile isotonic saline solution comprising a pharmaceutically acceptable salt of

2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethylamino)ethyl) formanilide (formoterol) or a hydrate thereof

and a citrate buffer,

wherein the concentration of the formoterol salt is equivalent to about 5-50 µg formoterol free base per mL of solution,

the dosage form is suitable for long term storage of the solution, and

the solution does not require dilution before the administration by nebulization of a therapeutically effective amount for bronchodilation of the formoterol salt to a human subject in need thereof.

119. A pharmaceutical composition according to claim 114, wherein the concentration of the formoterol salt is equivalent to about 5-10 µg formoterol free base per mL of solution.

120. A pharmaceutical composition according to claim 118, wherein the concentration of the formoterol salt is equivalent to about 5-10 µg formoterol free base per mL of solution.

* * * * *

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TO ALL TO WHOM THESE PRESENTS SHALL COME:

United States Patent and Trademark Office

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T. WALLACE
Certifying Officer



US006814953B2

(12) **United States Patent**
Banerjee et al.(10) **Patent No.:** **US 6,814,953 B2**(45) **Date of Patent:** **Nov. 9, 2004**(54) **BRONCHODILATING COMPOSITIONS AND METHODS**(75) Inventors: **Partha S. Banerjee**, Davis, CA (US);
Stephen Pham, Sacramento, CA (US);
Samuel O. Akapo, Vacaville, CA (US);
Imtiaz A. Chaudry, Napa, CA (US)(73) Assignee: **Dey L.P.**, Napa, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(21) Appl. No.: **10/138,866**(22) Filed: **May 3, 2002**(65) **Prior Publication Data**

US 2002/0151598 A1 Oct. 17, 2002

Related U.S. Application Data

(62) Division of application No. 09/887,281, filed on Jun. 22, 2001

(60) Provisional application No. 60/284,606, filed on Apr. 17, 2001.

(51) Int. Cl.⁷ **A61L 9/04**; **A61K 31/16**;
A61K 31/135(52) U.S. Cl. **424/45**; 514/630; 514/653(58) Field of Search 514/653, 630;
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(57) **ABSTRACT**

Bronchodilating compositions and methods are provided. The compositions are intended for administration as a nebulized aerosol. In certain embodiments, the compositions contain formoterol, or a derivative thereof. Methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders using the compositions provided herein are also provided.

146 Claims, No Drawings

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BRONCHODILATING COMPOSITIONS AND METHODS

RELATED APPLICATIONS

This application is a divisional application of U.S. application Ser. No. 09/887,281, to Banerjee et al., entitled "BRONCHODILATING COMPOSITIONS AND METHODS," filed Jun. 22, 2001. This application also claims the benefit of priority under 35 U.S.C. §119(e) to U.S. provisional patent application Ser. No. 60/284,606; filed Apr. 17, 2001, to Pham et al., entitled "BRONCHODILATING COMPOSITIONS AND METHODS." U.S. application Ser. No. 09/887,281 claims benefit of priority under 35 U.S.C. §119(e) to U.S. provisional patent application Ser. No. 60/284,606. The disclosures of the above-referenced applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Compositions and methods are provided relating to treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders. In particular, the compositions and methods herein include formoterol, and/or derivatives thereof. The compositions are propellant-free, sterile unit dose or multidose inhalation solutions intended for administration via nebulization.

BACKGROUND OF THE INVENTION

Bronchoconstrictive disorders affect millions worldwide. Such disorders include asthma (including bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness), chronic bronchitis and other chronic obstructive pulmonary diseases. Compounds having β_2 -adrenoreceptor agonist activity have been developed to treat these conditions. Such compounds include, but are not limited to, Albuterol (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); Bambuterol (dimethylcarbamic acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenylene ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)-methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetrahydro-1-((3,4,5-trimethoxyphenyl)methyl)-6,7-isquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); Fenoterol (5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)-amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methylethyl)amino)methyl)benzenemethanol); Hexoprenaline (4,4'-(1,6-hexanediyl)-bis(imino(1-hydroxy-2,1-ethanediyl)))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)-butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((1-methylethyl)-amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(2-pyridinyl)ethoxy)hexyl)amino)methyl)benzenemethanol); Pirbuterol (α^6 -(((1,1-dimethylethyl)amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol (((R*,S*)-(\pm)-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolinone); Reproterol ((7-(3-((2-(3,5-dihydroxyphenyl)-

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2-hydroxyethyl)amino)propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-((1R)-1-hydroxy-2-(N-((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)-carbostyryl hydrochloride).

These compounds are typically formulated for inhalation therapy. Aqueous or liquid formulations are preferred over solid formulations. Powdered formulations are more difficult to administer, particularly to the young and elderly who are most often the patients in need of such therapy. Compounds, such as formoterol, which has many desirable properties, are not adequately stable in aqueous solutions to be formulated as liquids. Hence there is a need for formulations of compounds, such as formoterol, in a form that can be conveniently administered and that are stable for extended periods of time. Therefore, it is an object herein to provide liquid formulations of μ_2 -adrenoreceptor agonist compounds. It is also an object herein to provide more stable formulations of others of these compounds.

SUMMARY OF THE INVENTION

Compositions and methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders are provided. The compositions provided herein are stable solutions of a bronchodilating agent, or a derivative thereof, in a pharmacologically suitable fluid that contains water, that are stable during long term storage. The compositions are suitable for direct administration to a subject in need thereof. Pharmacologically suitable fluids include, but are not limited to, polar fluids, including protic fluids. In certain embodiments herein, the compositions are aqueous solutions.

The compositions provided herein possess an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C. and greater than or equal to 1, 2 or 3 years storage time at 5° C. In certain of these embodiments, using Arrhenius kinetics, >80% or >85% or >90% or >95% estimated bronchodilating agent remains after such storage. These compositions are particularly useful for administration via nebulization. In certain embodiments herein, the subject is a mammal. In other embodiments, the subject is a human.

The compositions provided herein are formulated to remain stable over a relatively long period of time. For example, the compositions provided herein are stored between -15° C. and 25° C., or between 2° C. and 8° C., and remain stable for the desired time. In one embodiment, the compositions are stored at 5° C.

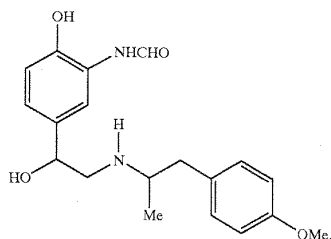
Among the bronchodilating agents for use herein are Albuterol (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); Bambuterol (dimethylcarbamic acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenylene ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetrahydro-1-((3,4,5-trimethoxyphenyl)methyl)-6,7-isquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -

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(((1,1-dimethylethyl)amino)methyl)benzenemethanol); Fenoterol (5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methylethyl)amino)methyl)benzenemethanol); Hexoprenaline (4,4'-(1,6-hexanediyloxy)-bis(imino(1-hydroxy-2,1-ethanediyloxy)))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(2-pyridinyl)ethoxy)hexyl)-amino)methyl)benzenemethanol); Pirbuterol (α^6 -(((1,1-dimethylethyl)-amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol ((R*,S*) (\pm)-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolinone); Reproterol ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)-propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)-amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-(((1R)-1-hydroxy-2-(N-((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)carbostyryl hydrochloride).

Of particular interest herein is formoterol, having the formula:



Formoterol for use in the compositions and methods provided herein includes 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof; and also includes the single enantiomers 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)-amino)ethyl)formanilide.

In certain embodiments, the compositions are administered via nebulization. Administration of a nebulized aerosol is preferred over the use of dry powders for inhalation in certain subject populations, including pediatric and geriatric groups.

In one embodiment, the compositions for use in the methods provided herein contain a pharmaceutically acceptable derivative of formoterol. In another embodiment, the compositions for use in the methods provided herein contain a pharmaceutically acceptable salt of formoterol. Pharmaceutically acceptable salts include, but are not limited to,

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salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. In one embodiment, the compositions for use in the methods provided herein contain formoterol fumarate or formoterol fumarate dihydrate. In another embodiment, the compositions for use in the methods provided herein contain formoterol tartrate.

Also provided herein are combinations containing a composition provided herein and a nebulizer. The combinations can be packaged as kits, which optionally contain other components, including instructions for use of the nebulizer. Any nebulizer is contemplated for use in the kits and methods provided herein. In particular, the nebulizers for use herein nebulize liquid formulations, including the compositions provided herein, containing no propellant. The nebulizer may produce the nebulized mist by any method known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or vibration. The nebulizer may further have an internal baffle. The internal baffle, together with the housing of the nebulizer, selectively removes large droplets from the mist by impaction and allows the droplets to return to the reservoir. The fine aerosol droplets thus produced are entrained into the lung by the inhaling air/oxygen.

Methods for the treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, including, but not limited to, asthma, including, but not limited to, bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness; chronic bronchitis; and other chronic obstructive pulmonary diseases are provided. The methods involve administering an effective amount of a pharmaceutical composition provided herein to a subject in need of such treatment.

Articles of manufacture, containing packaging material, a composition provided herein, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, are also provided.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, formoterol refers to 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof. The term formoterol also refers to the single enantiomers 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide.

As used herein, formoterol fumarate refers to a salt of formoterol having the formula (formoterol)* $\frac{1}{2}$ fumarate.

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As used herein, formoterol free base refers to the neutral, anhydrous form of formoterol. Thus, a recitation that a composition contains, e.g., 59 $\mu\text{g/mL}$ of formoterol free base means that the composition contains 59 $\mu\text{g/mL}$ of neutral, anhydrous formoterol. Such compositions may be prepared using a derivative of formoterol.

As used herein, an aerosol is liquid or particulate matter dispersed in air. Aerosols include dispersions of liquids, including aqueous and other solutions, and solids, including powders, in air.

As used herein, a nebulized solution refers to a solution that is dispersed in air to form an aerosol. Thus, a nebulized solution is a particular form of an aerosol.

As used herein, a nebulizer is an instrument that is capable of generating very fine liquid droplets for inhalation into the lung. Within this instrument, the nebulizing liquid or solution is atomized into a mist of droplets with a broad size distribution by methods known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or a vibrating orifice. Nebulizers may further contain, e.g., a baffle which, along with the housing of the instrument, selectively removes large droplets from the mist by impaction. Thus, the mist inhaled into the lung contains fine aerosol droplets.

As used herein, a pharmacologically suitable fluid is a solvent suitable for pharmaceutical use which is not a liquified propellant gas. Exemplary pharmacologically suitable fluids include polar fluids, including protic fluids such as water.

As used herein, a combination refers to any association between two or among more items.

As used herein, fluid refers to any composition that can flow. Fluids thus encompass compositions that are in the form of semi-solids, pastes, solutions, aqueous mixtures, gels, lotions, creams and other such compositions.

As used herein, a mixture is a mutual incorporation of two or more substances, without chemical union, the physical characteristics of each of the components being retained.

As used herein, the stability of a composition provided herein refers to the length of time at a given temperature that is greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient, e.g., formoterol, is present in the composition. Thus, for example, a composition that is stable for 30 days at 25° C. would have greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient present in the composition at 30 days following storage at 25° C.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxy-methyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such

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as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula $\text{C}=\text{C}(\text{OR})$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula $\text{C}=\text{C}(\text{OC}(\text{O})\text{R})$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecule, preferably 1 to about 100, more preferably 1 to about 10, most preferably one to about 2, 3 or 4, solvent or water molecules. Formoterol salts and hydrates are used in certain embodiments herein.

As used herein, treatment means any manner in which one or more of the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating cancer.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, a prodrug is a compound that, upon in vivo administration, is metabolized or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, e.g., Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

It is to be understood that the compounds for use in the compositions and methods provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds for use in the compositions provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization in vivo. Thus, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization in vivo, to administration of the compound in its (S) form.

As used herein, bronchoconstriction refers to a reduction in the caliber of a bronchus or bronchi.

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As used herein, undesired and/or uncontrolled bronchoconstriction refers to bronchoconstriction that results in or from a pathological symptom or condition. Pathological conditions include, but are not limited to, asthma and chronic obstructive pulmonary disease (COPD). Pathological symptoms include, but are not limited to, asthma and COPD.

As used herein, the statement that a composition is stable during "long term storage" means that the composition is suitable for administration to a subject in need thereof when it has an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C. and greater than or equal to 1, 2 or 3 years storage time at 5° C. In certain embodiments herein, using Arrhenius kinetics, >80% or >85% or >90% or >95% estimated bronchodilating agent remains after such storage.

A. Formoterol

Formoterol (2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide) is derived from adrenaline and, as noted above, is used as a β_2 -stimulator in inhalation therapy of respiratory diseases, particularly for the treatment of bronchial asthma. It has been reported that in patients with reversible obstructive respiratory diseases, formoterol has a bronchodilatory effect. This effect has a relatively rapid onset (approximately 1–3 minutes) and a relatively long duration (greater than 12 hours). Formoterol inhibits the release of leukotrienes and other messenger substances involved with inflammation, such as histamines. In addition, formoterol may bring about a hyperglycaemic activity.

To date, formoterol has been formulated as a dry powder and administered via devices such as the Turbuhaler® and the Aerolizer®. See, e.g., Seberova et al. (2000) *Respir. Med.* 94(6):607–611; Lotvall et al. (1999) *Can. Respir. J.* 6(5):412–416; Campbell et al. (1999) *Respir. Med.* 93(4):236–244; Nightingale et al. (1999) *Am. J. Respir. Crit. Care Med.* 159(6):1786–1790; Lecaillon et al. (1999) *Eur. J. Clin. Pharmacol.* 55(2):131–138; Bartow et al. (1998) *Drugs* 55(2):303–322; Ekstrom et al. (1998) *Respir. Med.* 92(8):1040–1045; Ringdal et al. (1998) *Respir. Med.* 92(8):1017–1021; Totterman et al. (1998) *Eur. Respir. J.* 12(3):573–579; Palmqvist et al. (1997) *Eur. Respir. J.* 10(11):2484–2489; Nielsen et al. (1997) *Eur. Respir. J.* 10(9):2105–2109; Ullman et al. (1996) *Allergy* 51(10):745–748; Selroos et al. (1996) *Clin. Immunother.* 6:273–299; and Schreurs et al. (1996) *Eur. Respir. J.* 9(8):1678–1683.

Formoterol is also available as a tablet and a dry syrup in certain areas of the world (e.g., Atcock®, marketed by Yamanouchi Pharmaceutical Co. Ltd., Japan). Formoterol formulations are also available in other areas (e.g., Europe and U.S.) for propellant-based metered dose inhalers and dry powder inhalers (e.g., Turbuhaler®, Aerolizer® and Foradil Aerolizer®). None of these formulations are water based. Sterile, stable, aqueous based inhalation solutions of formoterol for nebulization are not available, nor have they been reported.

Compositions containing formoterol in combination with other active ingredients have been disclosed. See, e.g., U.S. Pat. Nos. 6,004,537, 5,972,919 and 5,674,860 (formoterol and budesonide), 5,668,110, 5,683,983, 5,677,280 and 5,654,276 (formoterol and IL-5 inhibitors), 6,136,603 (formoterol and antisense modulators of IL-5), 5,602,110 (formoterol and millrinone), 5,525,623 (formoterol and a tryptase inhibitor), 5,691,336, 5,877,191, 5,929,094, 5,750,549 and 5,780,467 (formoterol and a tachykinin receptor antagonist); and International Patent Application Publication Nos. WO 99/00134 (formoterol and roflumilone) and WO 99/36095 (formoterol and a dopamine D₂ receptor agonist).

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Other compositions containing formoterol have been disclosed in U.S. Pat. Nos. 5,677,809, 6,126,919, 5,733,526, 6,071,971, 6,068,833, 5,795,564, 6,040,344, 6,041,777, 5,874,481, 5,965,622 and 6,161,536.

U.S. Pat. No. 6,150,418 discloses a "liquid active substance concentrate" containing formoterol in the form of its free base or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as active substance. This "liquid active substance concentrate" is reported to be a concentrated (i.e., greater than 10 mg/mL, preferably 75 to 500 mg/mL) solution or suspension that is stable for a period of several months possibly up to several years without any deterioration in the pharmaceutical quality. This patent teaches that it is the high concentration that allows for the stability of the concentrate. The "liquid active substance concentrate" is not suitable for direct administration to a patient.

U.S. Pat. No. 6,040,344 discloses an aqueous aerosol formulation of formoterol tartrate for use in a nebulizer. This patent states that the formulation disclosed therein is not attractive for long term storage.

B. Compositions for use in Treatment, Prevention, or Amelioration of one or More Symptoms of Bronchoconstrictive Disorders

Pharmaceutical compositions containing a β_2 -adrenoreceptor agonist for administration via nebulization are provided. The compositions are sterile filtered and filled in vials, including unit dose vials providing sterile unit dose formulations which are used in a nebulizer and suitably nebulized. Each unit dose vial is sterile and is suitably nebulized without contaminating other vials or the next dose.

The unit dose vials are formed in a form-fill-seal machine or by any other suitable method known to those of skill in the art. The vials may be made of plastic materials that are suitably used in these processes. For example, plastic materials for preparing the unit dose vials include, but are not limited to, low density polyethylene, high density polyethylene, polypropylene and polyesters. In one embodiment, the plastic material is low density polyethylene.

In one embodiment, the β_2 -adrenoreceptor agonist is formoterol, or a pharmaceutically acceptable derivative thereof. In other embodiments, the formoterol for use in the compositions provided herein is formoterol fumarate. Formoterol refers to 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof. The term formoterol also refers herein to the single enantiomers 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)-ethyl)formanilide.

In one embodiment, the compositions contain formoterol free base at a concentration of about 5 μ g/mL to about 2 mg/mL. In other embodiments, the maximum concentration of formoterol free base in the compositions is 1.5 mg/mL. In further embodiments, the concentration of formoterol free base in the compositions is about 10 μ g/mL to about 1 mg/mL, or about 50 μ g/mL to about 200 μ g/mL. In other embodiments, the compositions contain formoterol fumarate at a concentration of about 80 μ g/mL up to about 175 to 200 μ g/mL. In further embodiments, the compositions contain formoterol fumarate at a concentration of about 90 μ g/mL up to about 125 to 150 μ g/mL. The formoterol fumarate is formulated, in certain compositions provided herein, at a concentration of about 100 μ g/mL. The formoterol fumarate

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is formulated, in other compositions provided herein, at a concentration of about 85 $\mu\text{g/mL}$ or about 170 $\mu\text{g/mL}$. In one embodiment, the formoterol fumarate is formulated for single dosage administration via nebulization at a concentration of about 100 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol free base at a concentration of about 40 to about 150 $\mu\text{g/mL}$, particularly about 59 or about 118 $\mu\text{g/mL}$.

The compositions containing the β_2 -adrenoreceptor agonist, including formoterol, are formulated with a pharmacologically suitable fluid. Pharmacologically suitable fluids include, but are not limited to, polar solvents, including, but not limited to, compounds that contain hydroxyl groups or other polar groups. Such solvents include, but are not limited to, water or alcohols, such as ethanol, isopropanol, and glycols including propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol and polyoxyethylene alcohols.

Polar solvents also include protic solvents, including, but not limited to, water, aqueous saline solutions with one or more pharmaceutically acceptable salt(s), alcohols, glycols or a mixture thereof. For a saline solution as the solvent or as a component thereof, particularly suitable salts are those which display no or only negligible pharmacological activity after administration.

In the embodiments herein, the compositions have a pH of about 2.0 to about 8.0. In other embodiments, the compositions have a pH of about 4.0 to about 6.0, or about 4.5 to about 5.5. In certain of the above embodiments, the compositions are formulated at a pH of about 4, 4.4 or 4.6 up to about 5.5, 5.7 or 6. In other embodiments, the pH is about 5.0. It has been found herein that the rate constant for decomposition of an aqueous solution of formoterol is dependent on pH. The rate constant (k_{obs}) at 60° C. at a pH of 3, 4, 5 and 7 is approximately 0.62, 0.11, 0.044 and 0.55 day^{-1} , respectively. Therefore, the decomposition of formoterol in aqueous solution at 60° C. at a buffer concentration of 5 mM and an ionic strength of 0.05 is slowest at a pH of about 5.0.

The solubility of formoterol in aqueous solution has been found herein to be dependent on pH. Thus, at a pH of between about 5 and about 7, the aqueous solubility of formoterol at ambient temperature is approximately 2.2 mg/mL . At a pH of about 4, the aqueous solubility of formoterol at ambient temperature is approximately 3 mg/mL , while at a pH of about 3, the aqueous solubility of formoterol at ambient temperature is about 4.8 mg/mL . The solubility of formoterol in pure water, for example, high performance liquid chromatography (HPLC) water, at ambient temperature is approximately 2 mg/mL .

In other of the above embodiments, the compositions further contain a buffer, including, but not limited to, citric acid/phosphate, acetate, barbitol, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)

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piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), TRIZMAO (tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid)), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanedisulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), AMPD (2-amino-2-methyl-1,3-propanediol), and/or any other buffers known to those of skill in the art. In one embodiment, the buffer is citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer. In another embodiment, the buffer is a citrate buffer (citric acid/sodium citrate). The buffer concentration has been found herein to affect the stability of the composition. Buffer concentrations for use herein include from about 0 or 0.01 mM to about 150 mM, or about 1 mM to about 20 mM. In one embodiment, the buffer concentration is about 5 mM. In another embodiment, the buffer concentration is about 1 mM to about 50 mM, or about 20 mM. The kinetic-pH profile of formoterol is dependent on buffer concentration. At low and approximately neutral conditions, increasing the buffer concentration from 5 mM to 20 mM increased the rate constant of decomposition significantly. However, no noticeable differences in rate constant were observed in the pH region of about 4.5 to about 5.5 with increasing buffer concentration from 5 mM to 20 mM. The particular buffer and buffer concentration of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, e.g., the Examples).

The ionic strength of the compositions provided herein also has been found herein to affect the stability of the composition. Ionic strengths of the compositions provided herein are from about 0 to about 0.4, or from about 0.05 to about 0.16. Compositions having a lower ionic strength exhibit improved stability over formulations having higher strength of 0.2. The particular ionic strength of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, e.g., the Examples).

In embodiments where the pharmacologically suitable fluid is a saline solution, tonicity adjusting agents may be added to provide the desired ionic strength. Tonicity adjusting agents for use herein include those which display no or only negligible pharmacological activity after administration. Both inorganic and organic tonicity adjusting agents may be used in the compositions provided herein. Tonicity adjusting agents include, but are not limited to, ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium

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sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine and zinc sulfate. In certain embodiments, the tonicity adjusting agent is sodium chloride, which is present at a concentration of from about 0 mg/mL to about 10, 15 or 20 mg/mL. In further embodiments, the compositions contain sodium chloride at a concentration of from about 0 mg/mL to about 7.5 mg/mL. In another embodiment, the compositions contain sodium chloride at a concentration of 0 mg/mL, 1.5 mg/mL, 6.8 mg/mL or 7.5 mg/mL. In these embodiments, the pharmacologically suitable fluid is aqueous saline.

The storage temperature of the compositions provided herein also has been found herein to affect the stability of the composition. Compositions stored at a lower temperature exhibit improved stability over formulations stored at higher temperatures. The effect of temperature on the rate constant of decomposition at pH5, a buffer concentration of 5 mM, and an ionic strength of 0.05, was linear according to Arrhenius kinetics, i.e., when $\ln k_{obs}$ was plotted against $1/T$, where T is the temperature in degree Kelvin.

The estimated shelf-life of formoterol in the compositions provided herein is significantly greater than that reported for known formoterol compositions. The estimated shelf-life of formoterol in the compositions provided herein is about 6.2 years at 5° C. and about 7.5 months at 25° C. The estimated formoterol concentrations in the compositions provided herein as a function of storage time at 5° C. and usage time at 25° C. was determined. It is estimated that greater than 90% of the initial formoterol present in the composition remains after 3 months of usage time at 25° C. and 3 years of storage time at 5° C. as well as after 0.5 months of usage time at 25° C. and 1 year of storage time at 5° C.

In one embodiment, the compositions provided herein are prepared containing formoterol fumarate at a nominal concentration of 0.1 mg/mL at the indicated pH and citric acid/phosphate buffer concentrations. The solutions were stored at 60° C. In these compositions, formoterol is relatively more stable at a pH from about 4 to about 5, and is also more stable at lower buffer concentration.

The compositions provided herein also may include excipients and additives. The particular excipient or additive for use in the compositions for long term storage provided herein may be determined empirically using methods well known to those of skill in the art (see, e., the Examples). Excipients and additives are any pharmacologically suitable and therapeutically useful substance which is not an active substance. Excipients and additives generally have no pharmacological activity, or at least no undesirable pharmacological activity. The excipients and additives include, but are not limited to, surfactants, stabilizers, complexing agents, antioxidants, or preservatives which prolong the duration of use of the finished pharmaceutical formulation, flavorings, vitamins, or other additives known in the art. Complexing agents include, but are not limited to, ethylenediaminetetraacetic acid (EDTA) or a salt thereof, such as the disodium salt, citric acid, nitrilotriacetic acid and the salts thereof. In one embodiment, the complexing agent is EDTA. Preservatives include, but are not limited to, those that protect the solution from contamination with pathogenic particles, including benzalkonium chloride or benzoic acid, or ben-

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zoates such as sodium benzoate. Antioxidants include, but are not limited to, vitamins, provitamins, ascorbic acid, vitamin E or salts or esters thereof.

The compositions provided herein also may include a cosolvent, which increases the solubility of additives or the active ingredient(s). The particular cosolvent for use in the compositions for long term storage provided herein may be determined empirically using methods well known to those of skill in the art (see, e.g., the Examples). Cosolvents for use herein include, but are not limited to, hydroxylated solvents or other polar solvents, such as alcohols such as isopropyl alcohol, glycols such as propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol, and polyoxyethylene alcohols.

C. Preparation of Compounds for Use in the Compositions

The preparation of the compounds used in the compositions provided herein is described below. Any such compound or similar compound may be synthesized according to a method discussed in general below or by only minor modification of the methods by selecting appropriate starting materials.

Formoterol may be prepared according to the method disclosed in U.S. Pat. No. 3,994,974. Briefly, 4-benzyloxy-3-nitro- α -bromoacetophenone is reacted with N-benzyl-N-(1-methyl-2-p-methoxyphenylethyl)amine to form the α -aminoacetophenone. This compound was subjected to the following series of reactions: (i) reduction of the ketone with sodium borohydride; (ii) reduction of the nitro group with aqueous hydrochloric acid and iron powder; (iii) amine formylation with acetic anhydride and formic acid; and (iv) catalytic reduction over 10% palladium on carbon to afford formoterol free base. Crystallization of the Y.2 fumarate salt from ethanol provides (formoterol)* $\frac{1}{2}$ fumarate.

The individual enantiomers of formoterol, 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)-formanilide and 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide, may be prepared by the method disclosed in U.S. Pat. No. 6,040,344. Briefly, reaction of optically pure 4-benzyloxy-3-formamidostyrene oxide with an optically pure 4-methoxy- α -methyl-N-(phenylmethyl)benzenecethanamine, followed by debenzilation, affords the desired enantiomer of formoterol. Debenzilation may be accomplished by reduction with hydrogen gas in the presence of a noble metal catalyst, such as palladium on carbon.

The required optically pure 4-benzyloxy-3-formamidostyrene oxide may be prepared from 4-benzyloxy-3-nitro- α -bromoacetophenone by (i) reduction with vorane in the presence of an optically pure aminoindanol, (ii) hydrogenation over platinum oxide catalyst, (iii) formylation with formic acid and acetic anhydride, and (iv) epoxide formation in the presence of potassium carbonate.

The required optically pure 4-methoxy- α -methyl-N-(phenylmethyl)benzenecethanamine may be prepared from 4-methoxyphenylacetone by (i) reductive amination with benzylamine in the presence of hydrogen and a platinum catalyst, and (ii) crystallization of the desired optically pure amine from the resulting racemic mixture as its mandelic acid salt.

D. Formulation of Pharmaceutical Compositions

The compositions provided herein are prepared by procedures well known to those of skill in the art. For example, a formoterol fumarate solution may be prepared by the procedure of EXAMPLE 1. Briefly, a buffer solution having a pH and ionic strength of interest herein is prepared. In one

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embodiment, the buffer is a mixture of citric acid and sodium citrate, with sodium chloride added to achieve the desired ionic strength. Formoterol fumarate dihydrate is added to the buffer solution with agitation to produce a solution of the desired formoterol concentration. Exemplary formoterol concentrations are 0.17 g formoterol fumarate dihydrate/2 L and 0.34 g formoterol fumarate dihydrate/2 L buffer.

E. Evaluation of the Activity of the Compositions

Standard physiological, pharmacological and biochemical procedures are available for testing the compositions provided herein to identify those that possess bronchodilatory activity.

In vitro and in vivo assays that may be used to evaluate bronchodilatory activity are well known to those of skill in the art. See also, e.g., U.S. Pat. Nos. 3,994,974, and 6,068,833; German Patent No. 2,305,092; Kaumann et al. (1985) *Naunyn-Schmied Arch. Pharmacol.* 331:27-39; Lemoine et al. (1985) *Naunyn-Schmied Arch. Pharmacol.* 331:40-51; Tomioka et al. (1981) *Arch. Int. Pharmacodyn.* 250:279-292; Dellamary et al. (2000) *Pharm. Res.* 17(2):168-174; Rico-Mendez et al. (1999) *Rev. Alerg. Mex.* 46(5):130-135; Seberova et al. (2000) *Respir. Med.* 94(6):607-611; Lotvall et al. (1999) *Can. Respir. J.* 6(5):412-416; Campbell et al. (1999) *Respir. Med.* 93(4):236-244; Nightingale et al. (1999) *Am. J. Respir. Crit. Care Med.* 159(6):1786-1790; Lecaillon et al. (1999) *Eur. J. Clin. Pharmacol.* 55(2):131-138; Bartow et al. (1998) *Drugs* 55(2):303-322; Ekstrom et al. (1998) *Respir. Med.* 92(8):1040-1045; Ringdal et al. (1998) *Respir. Med.* 92(8):1017-1021; Totterman et al. (1998) *Eur. Respir. J.* 12(3):573-579; Palmqvist et al. (1997) *Eur. Respir. J.* 10(11):2484-2489; Nielsen et al. (1997) *Eur. Respir. J.* 10(9):2105-2109; Ullman et al. (1996) *Allergy* 51(10):745-748; Selroos et al. (1996) *Clin. Immunother.* 6:273-299; and Schreurs et al. (1996) *Eur. Respir. J.* 9(8):1678-1683.

F. Methods of Treatment of Bronchoconstrictive Disorders

The compositions provided herein are used for treating, preventing, or ameliorating one or more symptoms of a bronchoconstrictive disorders in a subject. In one embodiment, the method includes administering to a subject an effective amount of a composition containing a bronchodilating agent, including, but not limited to, formoterol, whereby the disease or disorder is treated or prevented. The subject treated is, in certain embodiments, a mammal. The mammal treated is, in certain embodiments, a human.

In another embodiment, the method provided herein includes oral administration of a composition provided herein. In certain embodiments herein, the composition is directly administered to a subject in need of such treatment via nebulization without dilution or other modification of the composition prior to administration.

The methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, in another embodiment, further include administering one or more of (a), (b), (c) or (d) as follows: (a) a β_2 -adrenoreceptor agonist; (b) a dopamine (D_2) receptor agonist; (c) a prophylactic therapeutic, such as a steroid; or (d) an anticholinergic agent; simultaneously with, prior to or subsequent to the composition provided herein.

β_2 -Adrenoreceptor agonists for use in combination with the compositions provided herein include, but are not limited to, Albuterol (α^1 -((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol; Bambuterol (dimethylcarbamate 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-

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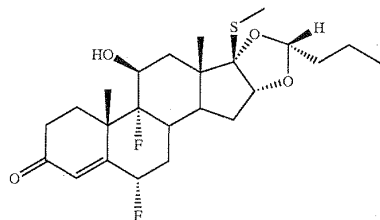
hydroxyethyl)-1,2-phenylene ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1, 2,3,4-tetrahydro-1-((3,4,5-trimethoxyphenyl)-methyl)-6, 7-isoquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); Fenoterol (5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methyl-ethyl)amino)methyl)benzenemethanol); Hexoprenaline (4,4'-(1,6-hexanediy)l-bis(imino(1-hydroxy-2,1-ethanediy)))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxy-2-((methyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(pyridinyl)ethoxy)hexyl)-amino)methyl)benzenemethanol); Pirbuterol (α^5 -(((1,1-dimethylethyl)-amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol (((R,S*)-(\pm))-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolinone); Reproterol (7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)-propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)-amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-((1R)-1-hydroxy-2-(N-((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)carbostyryl hydrochloride).

Dopamine (D_2) receptor agonists include, but are not limited to, Apomorphine ((r)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo[de,g]quinoline-10,11-diol); Bromocriptine ((5 α)-2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)ergotaman-3',6',18-trione); Cabergoline ((8 β)-N-(3-(dimethylamino)propyl)-N-((ethylamino)carbonyl)-6-(2-propenyl)ergoline-8-carboxamide); Lisuride (N'-((8 α)-9,10-didehydro-6-methylergolin-8-yl)-N,N-diethylurea); Pergolide ((8 β)-8-((methylthio)methyl)-6-propylergoline); Levodopa (3-hydroxy-L-tryrosine); Pramipexole ((s)-4,5,6,7-tetrahydro-N⁶-propyl-2,6-benzothiazolodiamine); Quinpirole hydrochloride (trans-(-)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo [3,4-g]quinoline hydrochloride); Ropinirole (4-(2-(dipropylamino)ethyl)-1,3-dihydro-2H-indol-2-one); and Talipexole (5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thiazolo [4,5-d]azepin-2-amine). Other dopamine D_2 receptor agonists for use herein are disclosed in International Patent Application Publication No. WO 99/36095.

Prophylactic therapeutics for use in combination therapy herein include steroidal anti-inflammatory agents, including, but not limited to, beclomethasone dipropionate (BDP), beclomethasone monopropionate (BMP), flunisolide, flutricamcinolone acetonide, dexamethasone, tipredane, ciclesonid, rofleponide, mometasone, mometasone furoate (Asmanex® Twisthaler™, Shering-Plough Corporation, Kenilworth, N.J.), RPR 106541, having the formula

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fluticasone or fluticasone propionate and budesonide or by way of sodium cromoglycate or nedocromil sodium.

Anticholinergic agents for use herein include, but are not limited to, ipratropium bromide, oxitropium bromide, atropine methyl nitrate, atropine sulfate, ipratropium, belladonna extract, scopolamine, scopolamine methobromide, homatropine methobromide, hyoscyamine, isopropamide, orphenadrine, benzalkonium chloride, tiotropium bromide and glycopyrronium bromide. In certain embodiments, the compositions contain an anticholinergic agent, such as ipratropium bromide or tiotropium bromide, at a concentration of about 5 µg/mL to about 5 mg/mL, or about 50 µg/mL to about 200 µg/mL. In other embodiments, the compositions for use in the methods herein contain an anticholinergic agent, including ipratropium bromide and tiotropium bromide, at a concentration of about 83 µg/mL or about 167 µg/mL.

Other active ingredients for use herein in combination therapy, include, but are not limited to, IL-5 inhibitors such as those disclosed in U.S. Pat. Nos. 5,668,110, 5,683,983, 5,677,280 and 5,654,276; antisense modulators of IL-5 such as those disclosed in U.S. Pat. No. 6,136,603; milrinone (1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile); milrinone lactate; tryptase inhibitors such as those disclosed in U.S. Pat. No. 5,525,623; tachykinin receptor antagonists such as those disclosed in U.S. Pat. Nos. 5,691,336, 5,877,191, 5,929,094, 5,750,549 and 5,780,467; leukotriene receptor antagonists such as montelukast sodium (Singular®, R-(E)-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]-propyl]thio]methyl]cyclopropanecarboxylic acid, monosodium salt), 5-lipoxygenase inhibitors such as zileuton (Zyflo®, Abbott Laboratories, Abbott Park, Ill.), and anti-IgE antibodies such as Xolair® (recombinant humanized anti-IgE monoclonal antibody (CGP 51901; IGE 025A; rhuMab-E25), Genentech, Inc., South San Francisco, Calif.).

The bronchoconstrictive disorder to be treated, prevented, or whose one or more symptoms are to be ameliorated is associated with asthma, including, but not limited to, bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness; and, particularly in embodiments where an anticholinergic agent is used, other chronic obstructive pulmonary diseases (COPDs), including, but not limited to, chronic bronchitis, emphysema, and associated cor pulmonale (heart disease secondary to disease of the lungs and respiratory system) with pulmonary hypertension, right ventricular hypertrophy and right heart failure. COPD is frequently associated with cigarette smoking, infections, environmental pollution and occupational dust exposure.

G. Nebulizers

The compositions provided herein are intended for administration to a subject in need of such treatment via nebulization. Nebulizers that nebulize liquid formulations contain-

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ing no propellant are suitable for use with the compositions provided herein. Nebulizers are available from, e.g., Pari GmbH (Starnberg, Germany), DeVilbiss Healthcare (Heston, Middlesex, UK), Healthdyne, Vital Signs, Baxter, Allied Health Care, Invacare, Hudson, Omron, Bremed, AirSep, Luminscope, Medisana, Siemens, Aerogen, Mountain Medical, Aerosol Medical Ltd. (Colchester, Essex, UK), AFP Medical (Rugby, Warwickshire, UK), Bard Ltd. (Sunderland, UK), Carri-Med Ltd. (Dorking, UK), Placem Nuiva (Brescia, Italy), Henleys Medical Supplies (London, UK), Intersurgical (Berkshire, UK), Lifecare Hospital Supplies (Leies, UK), Medic-Aid Ltd. (West Sussex, UK), Medix Ltd. (Essex, UK), Sinclair Medical Ltd. (Surrey, UK), and many others.

Nebulizers for use herein include, but are not limited to, jet nebulizers (optionally sold with compressors), ultrasonic nebulizers, and others. Exemplary jet nebulizers for use herein include Pari LC plus/ProNeb, Pari LC plus/ProNeb Turbo, Pari LC plus/Dura Neb 1000 & 2000, Pari LC plus/Walkhale, Pari LC plus/Pari Master, Pari LC star, Omron CompAir XL Portable Nebulizer System (NE-C18 and JetAir Disposable nebulizer), Omron CompAir Elite Compressor Nebulizer System (NE-C21 and Elite Air Reusable Nebulizer), Pari LC Plus or Pari LC Star nebulizer with Proneb Ultra compressor, Pulmo-aide, Pulmo-aide LT, Pulmo-aide traveler, Invacare Passport, Inspiration Healthdyne 626, Pulmo-Neb Traverler, DeVilbiss 646, Whisper Jet, Acorn II, Misty-Neb, Allied aerosol, Schuco Home Care, Lexan Plasic Pocet Neb, SideStream Hand Held Neb, Mobil Mist, Up-Draft, Up-Draft II, T Up-Draft, ISO-NEB, AVA-NEB, Micro Mist, and PulmoMate. Exemplary ultrasonic nebulizers for use herein include MicroAir, UltraAir, Siemens Ultra Nebulizer 145, CompAir, Pulmosonic, Scout, 5003 Ultrasonic Neb, 5110 Ultrasonic Neb, 5004 Desk Ultrasonic Nebulizer, Mystique Ultrasonic, Luminscope's Ultrasonic Nebulizer, Medisana Ultrasonic Nebulizer, Microstat Ultrasonic Nebulizer, and MABISMist Hand Held Ultrasonic Nebulizer. Other nebulizers for use herein include 5000 Electromagnetic Neb, 5001 Electromagnetic Neb 5002 Rotary Piston Neb, Lumineb I Piston Nebulizer 5500, Aeroneb™ Portable Nebulizer System, Aerodose™ Inhaler, and AeroEclipse Breath Actuated Nebulizer.

H. Articles of Manufacture

The compositions provided herein may be packaged as articles of manufacture containing packaging material, a composition provided herein, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in art. See, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

In one embodiment herein, the compositions are packaged with a nebulizer for direct administration of the composition to a subject in need thereof.

The following examples are included for illustrative purpose only and are not intended to limit the scope of the invention.

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EXAMPLE 1

Preparation of Formoterol Inhalation Solution Formulation

To a 5 L stainless steel vessel were added 0.68 g citric acid USP, 1.99 g sodium citrate USP, and 17.5 g sodium chloride USP. Purified water USP (2 L) was added to the stainless steel vessel and the contents were mixed with an overhead stirrer at a speed of 240 rpm for 10 minutes. Formoterol fumarate dihydrate (0.17 g for low dosage strength formulation, 0.34 g for high dosage strength formulation) was added and the solution was stirred at 240 rpm for 90 minutes.

EXAMPLE 2

Preparation of Formoterol Unit Dose Formulations

Following the procedure of EXAMPLE 1, the following formoterol unit dose formulations were prepared.

Low Strength (0.0085%)

A low strength formoterol unit dose formulation was prepared using the following reagents in the amounts indicated: formoterol fumarate dihydrate (0.170 mg), citric acid monohydrate, USP (0.68 mg), sodium citrate dihydrate, USP (1.99 mg), sodium chloride, USP (17.5 mg), and purified water, USP (qs to 2 mL).

High Strength (0.0170%)

A high strength formoterol unit dose formulation was prepared using the following reagents in the amounts indicated: formoterol fumarate dihydrate (0.340 mg), citric acid monohydrate, USP (0.68 mg), sodium citrate dihydrate, USP (1.99 mg), sodium chloride, USP (17.5 mg), and purified water, USP (qs to 2 mL).

EXAMPLE 3

Procedure for Stability Testing of Formoterol Solutions

Stability samples of the solutions prepared in EXAMPLES 1 and 2 were placed in scintillation vials with teflon-lined caps and stored in stability ovens at accelerated temperatures. At selected time points, aliquots of the samples were removed from the scintillation vials. The formoterol concentrations of the samples were analyzed by high performance liquid chromatography.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

What is claimed is:

1. A kit, comprising:
 - (a) a pharmaceutical composition, comprising formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof; and
 - (b) a nebulizer.
2. The kit of claim 1, wherein the composition has an estimated shelf-life of greater than 1 month usage time at 25° C. and greater than or equal to 1 year storage time at 5° C.
3. The kit of claim 2, wherein greater than about 80% of the initial formoterol is present after 1 month usage time at 25° C. and 1 year storage time at 5° C.
4. The kit of claim 1, wherein the composition further comprises a polar solvent.
5. The kit of the claim 4, wherein the polar solvent is a protic solvent.

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6. The kit of the claim 5, wherein the composition further comprises a tonicity adjusting agent.

7. The kit of claim 6, wherein the tonicity adjusting agent is ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine or zinc sulfate.

8. The kit of claim 7, wherein the tonicity adjusting agent is sodium chloride.

9. The kit of claim 1, wherein the composition further comprises a buffer.

10. The kit of claim 9, wherein the buffer is citric acid/phosphate, acetate, barbitol, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Pridaux-Ward, succinate, citrate-phosphate-borate (Teorelle-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), tris(hydroxymethylaminomethane, HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid)), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid)), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanedisulfonic acid)), TAPS (N-tris(hydroxy-methyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.

11. The kit of claim 10, wherein the buffer is citrate buffer.

12. The kit of claim 11, wherein the buffer concentration is from about 0.01 mM to about 150 mM.

13. The kit of claim 12, wherein the buffer concentration is from about 1 mM to about 20 mM.

14. The kit of claim 13, wherein the buffer concentration is about 5 mM.

15. The kit of claim 7, wherein the ionic strength of the composition is about 0 to about 0.4.

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16. The kit of claim 15, wherein the ionic strength of the composition is about 0.05 to about 0.16.

17. The kit of claim 1, wherein the pH of the composition is about 2.0 to about 8.0.

18. The kit of claim 17, wherein the pH of the composition is about 4.0 to about 6.0.

19. The kit of claim 18, wherein the pH of the composition is about 4.5 to about 5.5.

20. The kit of claim 19, wherein the pH of the composition is about 5.0.

21. The kit of claim 1, wherein the formoterol free base concentration in the composition is about 5 $\mu\text{g/mL}$ to about 2 mg/mL.

22. The kit of claim 21, wherein the formoterol free base concentration in the composition is about 10 $\mu\text{g/mL}$ to about 1 mg/mL.

23. The kit of claim 22, wherein the formoterol free base concentration in the composition is about 50 $\mu\text{g/mL}$ to about 200 $\mu\text{g/mL}$.

24. The kit of claim 23, wherein the formoterol free base concentration in the composition is about 59 $\mu\text{g/mL}$.

25. The kit of claim 23, wherein the formoterol free base concentration in the composition is about 118 $\mu\text{g/mL}$.

26. The kit of claim 7, wherein the composition further comprises a buffer.

27. The kit of claim 26, wherein the buffer is citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS ((N-morpholino)-butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid)), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid)), TRICINE (N-tris(hydroxy-methyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanedisulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.

28. The kit of claim 27, wherein the buffer is citrate buffer.

29. The kit of claim 28, wherein the buffer concentration is from about 0.01 mM to about 150 mM.

30. The kit of claim 29, wherein the buffer concentration is from about 1 mM to about 20 mM.

31. The kit of claim 30, wherein the buffer concentration is about 5 mM.

32. The kit of claim 26, wherein the ionic strength of the composition is about 0 to about 0.4.

33. The kit of claim 32, wherein the ionic strength of the composition is about 0.05 to about 0.16.

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34. The kit of claim 26, wherein the pH of the composition is about 2.0 to about 8.0.

35. The kit of claim 34, wherein the pH of the composition is about 4.0 to about 6.0.

36. The kit of claim 35, wherein the pH of the composition is about 4.5 to about 5.5.

37. The kit of claim 36, wherein the pH of the composition is about 5.0.

38. The kit of claim 26, wherein the formoterol free base concentration in the composition is about 5 $\mu\text{g/mL}$ to about 2 mg/mL.

39. The kit of claim 28, wherein the formoterol free base concentration in the composition is about 10 $\mu\text{g/mL}$ to about 1 mg/mL.

40. The kit of claim 39, wherein the formoterol free base concentration in the composition is about 50 $\mu\text{g/mL}$ to about 200 $\mu\text{g/mL}$.

41. The kit of claim 40, wherein the formoterol free base concentration in the composition is about 59 $\mu\text{g/mL}$.

42. The kit of claim 40, wherein the formoterol free base concentration in the composition is about 118 $\mu\text{g/mL}$.

43. The kit of claim 1, wherein the composition comprises (a) formoterol free base at a concentration of about 59 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

44. The kit of claim 1, wherein the composition comprises (a) formoterol free base at a concentration of about 118 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

45. The kit of claim 1, wherein the composition comprises (a) formoterol free base at a concentration of about 59 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 2 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

46. The kit of claim 1, wherein the composition comprises (a) formoterol free base at a concentration of about 118 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 2 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

47. The kit of claim 41, wherein the buffer is citrate buffer.

48. The kit of claim 41, wherein the buffer concentration is about 5 mM.

49. The kit of claim 41, wherein the ionic strength of the composition is about 0.005 to about 0.16.

50. The kit of claim 41, wherein the pH of the composition is about 5.0.

51. The kit of claim 41, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.005 to about 0.16; and the pH of the composition is about 5.0.

52. The kit of claim 42, wherein the buffer is citrate buffer.

53. The kit of claim 42, wherein the buffer concentration is about 5 mM.

54. The kit of claim 42, wherein the ionic strength of the composition is about 0.05 to about 0.16.

55. The kit of claim 42, wherein the pH of the composition is about 5.0.

56. The kit of claim 42, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

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57. The kit of claim 1, further comprising one or more of (a) to (j) as follows: (a) a β 2-adrenoreceptor agonist; (b) a dopamine (D2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lipoxygenase inhibitor; or (j) an anti-IgE antibody.

58. The kit of claim 10, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

59. The kit of claim 26, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

60. The kit of claim 12, wherein the buffer concentration is from about 1 mM to about 50 mM.

61. The kit of claim 60, wherein the buffer concentration is about 20 mM.

62. The kit of claim 29, wherein the buffer concentration is from about 1 mM to about 50 mM.

63. The kit of claim 62, wherein the buffer concentration is about 20 mM.

64. The kit of claim 41, wherein the buffer concentration is about 20 mM.

65. The kit of claim 41, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.01 to about 0.16; and the pH of the composition is about 5.0.

66. The kit of claim 42, wherein the buffer concentration is about 20 mM.

67. The kit of claim 42, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.01 to about 0.16; and the pH of the composition is about 5.0.

68. The kit of claim 1, further comprising an anticholinergic agent.

69. The kit of claim 68, wherein the anticholinergic agent is ipratropium bromide, oxitropium bromide, atropine methyl nitrate, tiotropium bromide or glycopyrronium bromide.

70. The kit of claim 69, wherein the anticholinergic agent is ipratropium bromide.

71. The kit of claim 70, wherein the ipratropium bromide is present at a concentration of about 5 μ g/mL to about 5 mg/mL.

72. The kit of claim 69, wherein the anticholinergic agent is tiotropium bromide.

73. The kit of claim 72, wherein the tiotropium bromide is present at a concentration of about 5 μ g/mL to about 5 mg/mL.

74. A method for the treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, comprising administering an effective amount of a pharmaceutical composition to a subject in need of such treatment, wherein the pharmaceutical composition comprises formoterol or a derivative thereof formulated at a concentration suitable for direct administration to a subject in need thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage and the fluid comprises water.

75. The method of claim 74, wherein the composition has an estimated shelf-life of greater than 1 month usage time at 25° C. and greater than or equal to 1 year storage time at 5° C.

76. The method of claim 75, wherein greater than about 80% of the initial formoterol is present after 1 month usage time at 25° C. and 1 year storage time at 5° C.

77. The method of claim 74, wherein the composition further comprises a polar solvent.

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78. The method of claim 77, wherein the polar solvent is a protic solvent.

79. The method of claim 78, wherein the composition further comprises a tonicity adjusting agent.

80. The method of claim 79, wherein the tonicity adjusting agent is ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine or zinc sulfate.

81. The method of claim 80, wherein the tonicity adjusting agent is sodium chloride.

82. The method of claim 74, wherein the composition further comprises a buffer.

83. The method of claim 82, wherein the buffer is citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Pradeaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)-butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid)), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid)), TRICINE (N-tris(hydroxy-methyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanedisulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.

84. The method of claim 83, wherein the buffer is citrate buffer.

85. The method of claim 84, wherein the buffer concentration is from about 0.01 mM to about 150 mM.

86. The method of claim 85, wherein the buffer concentration is from about 1 mM to about 20 mM.

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87. The method of claim 86, wherein the buffer concentration is about 5 mM.
88. The method of claim 87, wherein the ionic strength of the composition is about 0 to about 0.4.
89. The method of claim 88, wherein the ionic strength of the composition is about 0.05 to about 0.16.
90. The method of claim 74, wherein the pH of the composition is about 2.0 to about 8.0.
91. The method of claim 90, wherein the pH of the composition is about 4.0 to about 6.0.
92. The method of claim 91, wherein the pH of the composition is about 4.5 to about 5.5.
93. The method of claim 92, wherein the pH of the composition is about 5.0.
94. The method of claim 74, wherein the formoterol free base concentration in the composition is about 5 $\mu\text{g/mL}$ to about 2 mg/mL.
95. The method of claim 94, wherein the formoterol free base concentration in the composition is about 10 $\mu\text{g/mL}$ to about 1 mg/mL.
96. The method of claim 95, wherein the formoterol free base concentration in the composition is about 50 $\mu\text{g/mL}$ to about 200 $\mu\text{g/mL}$.
97. The method of claim 96, wherein the formoterol free base concentration in the composition is about 59 $\mu\text{g/mL}$.
98. The method of claim 96, wherein the formoterol free base concentration in the composition is about 118 $\mu\text{g/mL}$.
99. The method of claim 80, wherein the composition further comprises a buffer.
100. The method of claim 99, wherein the buffer is citric acid/phosphate, acetate, barbitol, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Pridaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)-butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid)), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid)), TRICINE (N-tris(hydroxy-methyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanedisulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.
101. The method of claim 100, wherein the buffer is citrate buffer.
102. The method of claim 101, wherein the buffer concentration is from about 0.01 mM to about 150 mM.
103. The method of claim 102, wherein the buffer concentration is from about 1 mM to about 20 mM.
104. The method of claim 103, wherein the buffer concentration is about 5 mM.

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105. The method of claim 99, wherein the ionic strength of the composition is about 0 to about 0.4.
106. The method of claim 105, wherein the ionic strength of the composition is about 0.05 to about 0.16.
107. The method of claim 99, wherein the pH of the composition is about 2.0 to about 8.0.
108. The method of claim 107, wherein the pH of the composition is about 4.0 to about 6.0.
109. The method of claim 108, wherein the pH of the composition is about 4.5 to about 5.5.
110. The method of claim 109, wherein the pH of the composition is about 5.0.
111. The method of claim 99, wherein the formoterol free base concentration in the composition is about 5 $\mu\text{g/mL}$ to about 2 mg/mL.
112. The method of claim 111, wherein the formoterol free base concentration in the composition is about 10 $\mu\text{g/mL}$ to about 1 mg/mL.
113. The method of claim 112, wherein the formoterol free base concentration in the composition is about 50 $\mu\text{g/mL}$ to about 200 $\mu\text{g/mL}$.
114. The method of claim 113, wherein the formoterol free base concentration in the composition is about 59 $\mu\text{g/mL}$.
115. The method of claim 113, wherein the formoterol free base concentration in the composition is about 118 $\mu\text{g/mL}$.
116. The method of claim 74, wherein the composition comprises (a) formoterol free base at a concentration of about 59 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.
117. The method of claim 74, wherein the composition comprises (a) formoterol free base at a concentration of about 118 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.
118. The method of claim 74, wherein the composition comprises (a) formoterol free base at a concentration of about 59 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 2 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.
119. The method of claim 74, wherein the composition comprises (a) formoterol free base at a concentration of about 118 $\mu\text{g/mL}$; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 2 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.
120. The method of claim 113, wherein the buffer is citrate buffer.
121. The method of claim 113, wherein the buffer concentration is about 5 mM.
122. The method of claim 113, wherein the ionic strength of the composition is about 0.05 to about 0.16.
123. The method of claim 113, wherein the pH of the composition is about 5.0.
124. The method of claim 113, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

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125. The method of claim 114, wherein the buffer is citrate buffer.

126. The method of claim 114, wherein the buffer concentration is about 5 mM.

127. The method of claim 114, wherein the ionic strength of the composition is about 0.05 to about 0.16.

128. The method of claim 114, wherein the pH of the composition is about 5.0.

129. The method of claim 114, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

130. The method of claim 74, further comprising administration of one or more of (a) to (j) as follows: (a) a β 2-adrenoreceptor agonist; (b) a dopamine receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lipoxygenase inhibitor; or (j) an anti-IgE antibody.

131. The method of claim 83, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

132. The method of claim 99, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

133. The method of claim 85, wherein the buffer concentration is from about 1 mM to about 50 mM.

134. The method of claim 133, wherein the buffer concentration is about 20 mM.

135. The method of claim 102, wherein the buffer concentration is from about 1 mM to about 50 mM.

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136. The method of claim 135, wherein the buffer concentration is about 20 mM.

137. The method of claim 114, wherein the buffer concentration is about 20 mM.

138. The method of claim 114, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

139. The method of claim 115, wherein the buffer concentration is about 20 mM.

140. The method of claim 115, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

141. The method of claim 74, further comprising an anticholinergic agent.

142. The method of claim 141, wherein the anticholinergic agent is ipratropium bromide, oxitropium bromide, atropine methyl nitrate, tiotropium bromide or glycopyrronium bromide.

143. The method of claim 142, wherein the anticholinergic agent is ipratropium bromide.

144. The method of claim 143, wherein the ipratropium bromide is present at a concentration of about 5 μ g/mL to about 5 mg/mL.

145. The method of claim 142, wherein the anticholinergic agent is tiotropium bromide.

146. The method of claim 145, wherein the tiotropium bromide is present at a concentration of about 5 μ g/mL to about 5 mg/mL.

* * * * *

Disclaimer

6,814,953 B2—Partha S. Banerjee, Davis, CA (US); Stephen Pham, Sacramento, CA (US); Samuel O. Akapo, Vacaville, CA (US); and Imtiaz A. Chaudry, Napa, CA (US). BRONCHODILATING COMPOSITIONS AND METHODS. Patent dated Nov. 9, 2004. Disclaimer filed July 8, 2005, by the assignee, Dey L.P. The term of this patent shall not extend beyond the expiration date of pat. No. 6,667,334.

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(54) **BRONCHODILATING COMPOSITIONS AND METHODS**

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(57) **ABSTRACT**

Bronchodilating compositions and methods are provided. The compositions are intended for administration as a nebulized aerosol. In certain embodiments, the compositions contain formoterol, or a derivative thereof. Methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders using the compositions provided herein are also provided.

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- Docket Sheet dated Aug. 8, 2010 in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, Mar. 21, 2007.
- Dey's Complaint in *Dey v. Sepracor* in the United States District Court for the Southern District of New York City, Civil Action No. 1:07-cv-2353, Mar. 21, 2007 (Dey).
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Reply to Second Amended Answer and Counterclaims in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, Feb. 12, 2009 (Dey) [Dey Confidential—Filed Under Seal].

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Dey's Reply to Sepracor's Amended Answer and Counterclaims to Dey's Supplemental Complaint in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, May 7, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Mylan's Reply to Sepracor's Amended Answer and Counterclaims to Dey's Supplemental Complaint in the United States District Court for the Southern District of New York, Civil Action No. 2:07-cv-2353, May 7, 2009 (Dey) [Dey Confidential—Filed Under Seal].

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Dey's Reply to Sepracor's Answer and Counterclaims to Dey's Second Supplemental Complaint in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, Jul. 8, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Mylan's Reply to Sepracor's Answer and Counterclaims to Dey's Second Supplemental Complaint in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, Jul. 8, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Dey's Supplemental Objections and Responses to Sepracor's First Set of Interrogatories to Dey in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Dey's Objections and Responses to Sepracor's First Set of Interrogatories in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Dey and Mylan's Objections and Responses to Sepracor's Third Set of Interrogatories in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron, Sep. 25, 2009 (Sepracor) [Dey Confidential—Filed Under Seal] [Sepracor Confidential—Redacted].

Opening Expert Report of Peter Byron Exhibit 1: Curriculum Vitae of Peter Byron (Sepracor).

Opening Expert Report of Peter Byron Exhibit 2: List of Documents Considered (Sepracor).

Opening Expert Report of Peter Byron Exhibit 3: U.S. Patent No. 6,667,344 (currently under reexamination, Control No. 90/010,488) (provided as Document A129).

Opening Expert Report of Peter Byron Exhibit 4: U.S. Patent No. 6,814,953 (currently under reexamination, Control No. 90/010,489) (provided as Document A133).

Opening Expert Report of Peter Byron Exhibit 5: U.S. Patent No. 7,348,362 (provided as Document A136).

Opening Expert Report of Peter Byron Exhibit 6: U.S. Patent No. 7,462,645 (provided as Document A137).

Opening Expert Report of Peter Byron Exhibit 7: U.S. Patent No. 7,465,756 (provided as Document A138).

Opening Expert Report of Peter Byron Exhibit 8: U.S. Patent No. 7,473,710 (provided as Document A139).

Opening Expert Report of Peter Byron Exhibit 9: U.S. Patent No. 7,541,385 (provided as Document A140).

Opening Expert Report of Peter Byron Exhibit 10: U.S. Patent No. 3,994,974 (provided as Document A23).

Opening Expert Report of Peter Byron Exhibit 11: *Aerosols in Medicine: Principles, Diagnosis and Therapy*. (ed. by Moren, F., Dolovich, M.B., Newhouse, M.T. and Newman, S.P., Second, revised edition, pp. 340–350 1993).

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Opening Expert Report of Peter Byron Exhibit 15: Pharmaceutical Development Report for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 16: PCT Publication WO 01/39745 (provided as Document B59).

Opening Expert Report of Peter Byron Exhibit 17: U.S. Patent No. 6,667,344 (provided as Document A129).

Opening Expert Report of Peter Byron Exhibit 18: Response to Office Action, dated Apr. 22, 2003 in U.S. Appl. No. 09/887,281.

Opening Expert Report of Peter Byron Exhibit 19: Summary of Formoterol work done by M. Joyce (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 20: U.S. Patent No. 6,150,418 (provided as Document A93).

Opening Expert Report of Peter Byron Exhibit 21: Lachman, L., et al., *The Theory and Practice of Industrial Pharmacy*, (Third edition, pp. 176, 191–193, 761–770) (1986).

Opening Expert Report of Peter Byron Exhibit 22: Summary of Formoterol Unit Dose Formulation Development (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 23: First Banerjee Deposition Transcript, Feb. 13, 2009 (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 24: Oral Inhalation PDT Meeting Minutes Nov. 9, 2000 (Sepracor) [Dey Confidential—Filed Under Seal].

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Opening Expert Report of Peter Byron Exhibit 25: U.S. Patent No. 6,161,536 (provided as Document A95).

Opening Expert Report of Peter Byron Exhibit 26: Effect Of Surfactants And Cosolvents On Formoterol Stability (Sepracor) [Day Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 27: A Comparative Stability Study Of Formoterol In Active Substance Concentrate (U.S. Patent #6,150,418) And Dey's Formoterol Fumarate Inhalation Solutions (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 28: Akapo Deposition Transcript, Dec. 10, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 29: Letter of May 12, 2009 from Teva Parenteral to Dey LP: Notice of ANA 91-141 Concerning Formoterol Fumarate Inhalation Solution, 0.02 mg/2mL With Paragraph IV Certification Concerning U.S. Patent Nos. 6,667,344, 6,814,953, 7,348, 362 and 7,462,645 (Teva) [Teva Confidential—Filed Under Seal].

Opening Expert Report of Peter Bryan Exhibit 30: Ionic Strength Calculations (Sepracor) [Sepracor Confidential—Redacted] [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 31: Formoterol: Merck Index (Twelfth Edition, p. 4273) (1996).

Opening Expert Report of Peter Byron Exhibit 32: Canadian Patent No. 2,257,329.

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Opening Expert Report of Peter Byron Exhibit 35: Pham Deposition Transcript, Sep. 9, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 36: Formoterol Unit Dose Preliminary Results and Formulation Plan. (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 37: Vodas, E.B., *Stability of Pharmaceutical Products*. (Remington, Nineteenth Edition, vol. 1) Ch. 38, pp. 639-647 (1995).

Opening Expert Report of Peter Byron Exhibit 38: U.S. Appl. No. 60/061,363.

Opening Expert Report of Peter Byron Exhibit 39: Decision on Petition dated Oct. 8, 2002 in U.S. Appl. No. 09/887,281.

Opening Expert Report of Peter Byron Exhibit 40: Table Comparing the Claims of the '344 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 41: Table Comparing the Claims of the '953 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 42: Table Comparing the Claims of the '362 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 43: Table Comparing the Claims of the '385 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 44: Table Comparing the Claims of the '645 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 45: Table Comparing the Claims of the '710 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 46: Table Comparing the Claims of the '756 patent to the prior art, for Obviousness (Sepracor).

Opening Expert Report of Peter Byron Exhibit 47: Resenborg, J., et al., *Mass Balance and Metabolism of P_{H1} Formoterol in Healthy Men After Combined I.V. and Oral Administration Mimicking Inhalation*. Drug Metabolism and Disposition 27(10): 1104-1116 (1999).

Opening Expert Report of Peter Byron Exhibit 48: Formoterol Fumarate Formulation Activities (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 49: (Sepracor) [Dey Confidential—Filed Under Seal] Missing Still Need Document.

Opening Expert Report of Peter Byron Exhibit 50: Laskar Deposition Transcript, Sep. 11, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 80: Dey's Supplemental Objections and Responses to Sepracor's First Set of Interrogatories to Dey. (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 91: Dey's and Mylan's Objections and Responses to Sepracor's Third Set of Interrogatories. (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 97: Second Chaudry Deposition Transcript, Jul. 1, 2009. (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 98: Formoterol, Formoterol Concentrate, and Formoterol Low Volume Pls (Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Peter Byron Exhibit 99: Declaration of P. Banerjee dated Sep. 24, 2004 submitted in U.S. Appl. No. 09/887,496.

Rebuttal Expert Report of Peter Byron, Oct. 23, 2009 (Sepracor) [Dey Confidential—Filed Under Seal] [Sepracor Confidential—Redacted].

Rebuttal Expert Report of Peter Byron Exhibit 100: Amendment After Final dated Apr. 22, 2003, submitted in U.S. Appl. No. 09/887,281.

Rebuttal Expert Report of Peter Byron Exhibit 101: Notice of Allowance.

Rebuttal Expert of Peter Byron Exhibit 102: Akapo Deposition Transcript, Dec. 10, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

Rebuttal Expert Report of Peter Byron Exhibit 103: Laskar Deposition Transcript, Sep. 11, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].

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Reply Expert Report of Peter Byron, Nov. 20, 2009 (Sepracor) [Dey Confidential—Filed Under Seal] [Sepracor Confidential—Redacted].

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- Reply Expert Report of Peter Byron Exhibit 108: Foral, P.A., et al., *Nebulized Opioids Use in COPD*. Chest 125:691-694 (2004).
- Reply Expert Report of Peter Byron Exhibit 109: Second Chaudry Deposition Transcript, Jul. 1, 2009 (Sepracor) [Dey Confidential—Filed Under Seal].
- Reply Expert Report of Peter Byron Exhibit 110: Laskar Deposition Transcript, Sep. 11, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].
- Reply Expert Report of Peter Byron Exhibit 111: Amendment dated Mar. 23, 2007, submitted in U.S. Appl. No. 10/887,785.
- Reply Expert Report of Peter Byron Exhibit 112: Rieger Deposition Transcript, Aug. 19, 2009 (Sepracor) [Dey Confidential—Filed Under Seal].
- Reply Expert Report of Peter Byron Exhibit 113: Fluorouracil® Package Insert.
- Reply Expert Report of Peter Byron Exhibit 114: Buffered Pfizerpen® Instructions.
- Reply Expert Report of Peter Byron Exhibit 115: Interoffice Memo from G. Michaud to M. Engle, Apr. 4, 2002 (Sepracor) [Dey Confidential—Filed Under Seal].
- Reply Expert Report of Peter Byron Exhibit 118: Akapo Deposition Transcript, Dec. 10, 2008 (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Peter Byron—noted in Exhibit 2: *Handbook of Pharmaceutical Excipients*, 3rd Ed., (ed. Kibbe, A.H.), "Citric Acid Monohydrate," pp. 140-142 (2000).
- Expert Report of Dr. Gene Colice, Nov. 20, 2009 (Dey).
- Expert Report of Dr. Gene Colice Exhibit 1: Curriculum Vitae for Dr. Gene Colice (Dey).
- Expert Report of Dr. Gene Colice Exhibit 2: Testifying Case List for Dr. Gene Colice (Dey).
- Expert Report of Dr. Gene Colice Exhibit 3: List of Documents Considered (Dey).
- Expert Report of Dr. Gene Colice Exhibit 4: Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease—Updated 2008.
- Expert Report of Dr. Gene Colice Exhibit 5: Dolovich et al., *Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines*. Chest 2005; 127: 335-371.
- Expert Report of Dr. Gene Colice Exhibit 6: Nebulizers—Perforomist and Brovana—Coverage Criteria and Billing Instructions. TriCenturion Bulletin, Aug. 2007.
- Expert Report of Hon. Gerald Mossinghoff, Oct. 23, 2009 (Dey) [Dey Confidential—Filed Under Seal].
- Expert Report of Hon. Gerald Mossinghoff Exhibit A: Curriculum Vitae for Hon. Gerald Mossinghoff (Dey).
- Expert Report of Hon. Gerald Mossinghoff Exhibit B: Publications of Hon. Gerald Mossinghoff (Dey).
- Expert Report of Hon. Gerald Mossinghoff Exhibit C: The Hon. Gerald Mossinghoff Appeared as a Principal Witness in the Following Congressional Hearings (Dey).
- Expert Report of Hon. Gerald Mossinghoff Exhibit D: Patent Cases in which the Hon. Gerald Mossinghoff Testified as an Expert Witness in Court or in a Deposition (Dey).
- Expert Report of Hon. Gerald Mossinghoff Exhibit E: List of Documents Considered (Dey).
- Expert Report of Hon. Gerald Mossinghoff—noted in Exhibit E: Letter from Jeffery Alan Hovden to David M. Conca, Jul. 22, 2008.
- Rebuttal Expert Report Lehman, Oct. 22, 2009 [Sepracor Confidential—Redacted] [Dey Confidential—Filed Under Seal].
- Rebuttal Expert Report of Lehman Exhibit 1: List of Documents Considered.
- Rebuttal Expert Report of Lehman Exhibit 2: Maesen, F.P.V., et al., *Formoterol Suspension Aerosol Comparison with Formoterol Solution Aerosol for 12 Weeks in Asthmatic Patients*. Chest 102:1544-1549 (1992) (provided as Document C445).
- Rebuttal Expert Report of Lehman Exhibit 3: U.S. Patent No. 6,150,418 (provided as Document A93).
- Rebuttal Expert Report of Lehman Exhibit 4: A Comparative Stability Study Of Formoterol in Active Substance Concentrate (US Patent #6, 150,418 [to Hochrainer et al.]) and Dey's Formoterol Fumarate Inhalation Solutions Oct. 10, 2005 [Dey Confidential—Filed Under Seal].
- Rebuttal Expert Report of Lehman Exhibit 5: Declaration of P. Banerjee dated Sep. 24, 2004 submitted in U.S. Appl. No. 09/887,496 (Dey).
- Rebuttal Expert Report of Lehman Exhibit 6: U.S. Patent No. 3,994,974 (provided as Document A23).
- Rebuttal Expert Report of Lehman Exhibit 7: U.S. Patent No. 6,040,344 (provided as Document A85).
- Rebuttal Expert Report of Lehman Exhibit 8: Guidance for Industry: Analytical Procedures and Methods Validation—Draft Guidance, Aug. 2000.
- Rebuttal Expert Report of Lehman Exhibit 9: NDA Analytical Procedures (Formoterol Fumarate Inhalation Solution, 20 mcg/2 ML (Dey) [Dey Confidential—Filed Under Seal].
- Rebuttal Expert Report of Lehman Exhibit 12: Foradil®.
- Rebuttal Expert Report of Lehman Exhibit 13: European Patent No. 1 157 689 (provided as Document B7).
- Rebuttal Expert of Lehman Exhibit 14: Formoterol Inhalation Unit Dose (Dey) [Dey Confidential—Filed Under Seal].
- Expert Report of Robert Kuhn, Oct. 23, 2009 (Dey).
- Expert Report of Robert Kuhn Exhibit 1: U.S. Patent No. 3,994,974 (provided as Document A23).
- Expert Report of Robert Kuhn Exhibit 2: Curriculum Vitae for Robert Kuhn (Dey).
- Expert Report of Robert Kuhn Exhibit 3: List of Materials Reviewed (Dey).
- Expert Report Kuhn Exhibit 4: Kuhn, R., *Formulation of Aerosolized Therapeutics* Chest 120 (2001) 94S-98S.
- Expert Report of Robert Kuhn Exhibit 5: Guhan et al., *Systemic effects of formoterol and salmeterol: a dose-response comparison in healthy subjects*. Thorax 55 (2000) 650-656.
- Expert Report of Robert Kuhn Exhibit 6: Kuhn, R., *Pharmaceutical Considerations in Aerosol Drug Delivery* Pharmacotherapy 22 (2002) 80S-85S.
- Expert Report of Robert Kuhn Exhibit 7: Walsh, *Pharmaceutical Biotechnology: Concepts and Applications*, John Wiley & Sons, Ltd., West Sussex, England, 2007, p. 72.
- Expert Report of Robert Kuhn Exhibit 8: Hickey, A.J., *Pharmaceutical Inhalation Aerosol Technology*, Marcel Dekker Inc., New York, Ed. 2, 2004, p. 282.
- Expert Report of Robert Kuhn Exhibit 9: FDA CDER Transcript, Meeting of Pharmacy Compounding Advisory Committee, Sep. 14, 1998, p. 136-139.
- Expert Report of Robert Kuhn Exhibit 10: Molema et al., *Drug Targeting Organ-Specific Strategies*, Wiley-VCH, New York, 2001, p. 67.

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Expert Report of Robert Kuhn Exhibit 12: Garg et al., *Insulin Delivery via Lungs—Is It Still Possible?* *Diabetes Technology & Therapeutics* 11, Suppl. 2 (2009) S-1.

Opening Expert Report of Larry Nixon, Sep. 25, 2009—(Sepracor) [Dey Confidential—Filed Under Seal].

Opening Expert Report of Larry Nixon Exhibit 1: Documents Considered.

Opening Expert Report of Larry Nixon Exhibit 2: Curriculum Vitae for Larry Nixon.

Reply Expert Report of Larry Nixon, Nov. 20, 2009 (Sepracor) [Dey Confidential—Filed Under Seal].

Reply Expert Report of Larry Nixon Exhibit 1: United States Patent and Trademark Office Utility, Plant, and Reissue Examiner Staffing FY 2009.

Reply Expert Report of Larry Nixon Exhibit 2: List of Documents Considered.

Reply Expert of Larry Nixon Exhibit 3: United States Patent and Trademark Office Performance and Accountability Report FY 2009.

Opening Expert Report of Dr. Philip Marcus, Oct. 23, 2009 (Sepracor).

Opening Expert Report of Dr. Philip Marcus Exhibit 1: Curriculum Vitae for Dr. Philip Marcus.

Opening Expert Report of Dr. Philip Marcus Exhibit 2: Cases Testified in over the last Four Years.

Opening Expert Report of Dr. Philip Marcus Exhibit 3: List of Documents Considered.

Opening Expert Report of Dr. Philip Marcus Document Reviewed: Dolovich, M.B., et al., *Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines*. *Chest* 127:335–371 (2005).

Opening Expert Report of Dr. Philip Marcus Document Reviewed: Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease—Updated 2008.

Opening Expert Report of Dr. Philip Marcus Document Reviewed: Standards for the Diagnosis and Management of Patients with COPD (2004).

Reply Expert Report of Dr. Philip Marcus, Nov. 20, 2009.

Reply Expert Report of Dr. Philip Marcus Exhibit 1: List of Documents Considered.

Supplemental Expert Report of Dr. Gordon Rausser, PhD, Oct. 22, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Supplemental Expert Report of Dr. Gordon Rausser Exhibit A: Four Year Testimony List of Gordon Rausser (Dey).

Supplemental Expert Report of Dr. Gordon Rausser Exhibit B: Additional Materials Reviewed and Relied On (Dey).

Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Label for Perforomist.

Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Label for Brovana.

Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Grove, C., *Availability of Xopenex and Brovana for Medicare Patients*. Associated Content, Sep. 17, 2007, www.associatedcontent.com/article/372751/availability_of_xopenex_and_brovana.html?cat=71 (last visited Jul. 26, 2010).

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Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Narayanan, S., et al., *Temporal Differences in the Role of Marketing Communication in New Product Categories*, *Journal of Marketing Research* 42 (Aug. 2005) pp. 278–290.

Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Navarro, R.P. *Pharmacy & Therapeutics Committees in managed care organizations*, in Robert P. Navarro, ed., *Managed Care Pharmacy Practice*, Sudbury, Mass.: Jones and Bartlett Publishers, pp. 323–340.

Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Berndt, E.R., et al., *The roles of Marketing, product quality and price competition in the growth and composition of the US antiulcer drug industry*, in *The Economics of New Goods*, ed. Timothy Bresnahan and Robert J. Gordon (Chicago: University of Chicago Press, 1997).

Supplemental Expert Report of Dr. Gordon Rausser Cited in Report: Rosental, M.B., et al., *Derrand Effects of Recent Changes in Prescription Drug Promotion*, Kaiser Family Foundation, Jun. 2003.

Expert Report of Carlos Schuler, Oct. 23, 2009 (Dey).

Expert Report of Carlos Schuler Exhibit 1: Curriculum Vitae for Carlos Schuler (Dey).

Expert Report of Carlos Schuler Exhibit 2: List of Documents Considered (Dey).

Expert Report of Carlos Schuler Exhibit 3: Brovana® labeling and Medication Guide.

Expert Report of Carlos Schuler Exhibit 4: Perforomist® labeling and Medication Guide.

Expert Report of Carlos Schuler Exhibit 5: Foradil® labeling.

Expert Report of Carlos Schuler Exhibit 6: U.S. Patent No. 6,150,418 (provided as Document A93).

Expert Report of Carlos Schuler Exhibit 7: Dalby, R.; Spallek, M.; Voshaar, T., *A Review of the Development of Respimat® Soft Mist™ Inhaler*, *International Journal of Pharmaceutics* 283 (2004) 1–9.

Expert Report of Carlos Schuler Exhibit 8: Respimat® promotional materials (located at <http://www.respimat.com/com/homepage.jsp>), last visited Jul. 15, 2010.

Expert Report of Carlos Schuler Exhibit 9: Pari Nebulizer.

Expert Report of Carlos Schuler Exhibit 10: Spriva® User Guide.

Expert Report of Carlos Schuler Exhibit 11: PCT Publication WO91/14468.

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- Expert Report of Carlos Schuler Exhibit 12: PCT Publication WO97/12687.
- Expert Report of Carlos Schuler Exhibit 13: U.S. Patent No. 7,571,722.
- Expert Report of Carlos Schuler Exhibit 14: Zierenberg, et al., *Boehringer Ingelheim Nebulizer Bineb® A New Approach to Inhalation Therapy*. Respiratory Drug Delivery V, 1996 (p. 187-193).
- Expert Report of Carlos Schuler Exhibit 15: PCT Publication WO97/39831.
- Expert Report of Carlos Schuler Exhibit 16: German Patent Publication DE 198 47 968.
- Expert Report of Carlos Schuler Exhibit 17: US Patent No. 6,481,435 (provided as Document A125).
- Expert Report of Carlos Schuler Exhibit 18: Spallek, M.W., et al., *Scale-Up And Production Challenges Of Bringing Respimat® Soft Mist™ Inhaler (SIM) To Market* Respiratory Drug Delivery IX, 2004 (p. 263-270).
- Expert Report of Carlos Schuler Exhibit 19: Clark et al., *Formulation of Proteins for Pulmonary Delivery*. Protein Formulation and Delivery Second Edition (Drugs and the Pharmaceutical Sciences), p. 219-253.
- Expert Report of Carlos Schuler Exhibit 20: Kunkel, G. et al., *Respimat® (a New Soft Mist Inhaler) Delivering Fenoterol plus Ipratropium Bromide Provides Equivalent Bronchodilation at Half the Cumulative Dose Compared with a Conventional Metered Dose Inhaler in Asthmatic Patients*. Respiration 2000;67:306-314.
- Expert Report of Carlos Schuler Exhibit 21: Ganderton, D., *Targeted delivery of inhaled drugs: current challenges and future goals*. J Aerosol Med., 12 (suppl. 1), pp. 3-8 (1999).
- Expert Report of Carlos Schuler Exhibit 22: Goldberg et al., *Improved delivery of fenoterol plus ipratropium bromide using Respimat® compared with a conventional metered dose inhaler*. Eur Respir J 2001; 17: 225-232.
- Expert Report of Carlos Schuler Exhibit 25: Vincken et al., *Fenoterol Delivery by Respimat® Soft Mist Inhaler Versus CFC Metered Dose Inhaler, Cumulative Dose-Response Study in Asthma Patients*. Journal of Asthma, vol. 40, No. 6 pp. 721-730 (2003).
- Expert Report of Carlos Schuler Exhibit 24: Vincken et al., *Long Term Efficacy and Safety of Ipratropium Bromide plus Fenoterol via Respimat® Soft Mist™ Inhaler (SIM) versus a Pressurized Metered-Dose Inhaler in Asthma*. Clin. Drug. Invest. 2004;24 (1): 17-28.
- Expert Report of Carlos Schuler Exhibit 25: Hochrainer et al., *Comparison of the Aerosol Velocity and Spray Duration of Respimat® Soft Mist™ Inhaler and Pressurized Metered Dose Inhalers*. J. Aerosol Medicine 2005, vol. 18, No. 3, pp. 273-282.
- Opening Expert Report of Robert Williams III, Sep. 25, 2009.
- Opening Expert Report of Robert Williams III Exhibit 1: Curriculum Vitae for Robert Williams III.
- Opening Expert Report of Robert Williams III Exhibit 2: U.S. Patent No. 3,994,974 (provided as Document A23).
- Opening Expert Report of Robert Williams III Exhibit 3: U.S. Patent No. 6,040,344 (provided as Document A85).
- Opening Expert Report of Robert Williams III Exhibit 4: Byron, P.R., *Aerosol Formulation, Generation, and Delivery Using Nonmetered Systems*, Respiratory Drug Delivery, Ch. 6, pp. 143-165.
- Opening Expert Report of Robert Williams III Exhibit 5: "Sodium Hydroxide," The Merck Index, 12th Ed., pp. 8772-8773 (1996).
- Opening Expert Report of Robert Williams III Exhibit 6: : *Aerosols in Medicine: Principles, Diagnosis and Therapy*. (ed. by Moren, F., Dolovich, M.B., Newhouse, M.T. and Newman, S.P., Second, revised edition, pp. 340-350 1993).
- Opening Expert Report of Robert Williams III Exhibit 7: Stoklosa, M.J. et al., *Pharmaceutical Calculations*, 7th Ed., pp. 196-197 (1980).
- Opening Expert Report of Robert Williams III Exhibit 8: *Handbook of Pharmaceutical Excipients*, 3rd Ed., (ed. Kibbe, A.H.), "Citric Acid Monohydrate," pp. 140-142 (2000).
- Opening Expert Report of Robert Williams III Exhibit 9: *Pharmaceutical Inhalation Aerosol Technology*. (ed. by Hickey, A.J.), 54: 166-167 (1992).
- Opening Expert Report of Robert Williams III Exhibit 10: Formoterol Fumarate Inhalation Solution 20 mcg/2mL Pharmaceutical Development Report (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 11: Formoterol Fumarate Inhalation Solution 20 mcg/2mL Analytical Procedures (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 13: GAO Arformoterol Tartrate and Murakami Fumarate Tables.
- Opening Expert Report of Robert Williams III Exhibit 14: GAO Arformoterol Tartrate and Murakami Fumarate Tables.
- Opening Expert Report of Robert Williams III Exhibit 15: Study Report Dey Formoterol Fumarate vs. U.S. Patent No. 6,150,418 (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 16: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 17: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 18: Stability Data of Formoterol Low Drug Concentration (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 19: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 20: Effect of pH on Degradation of Formoterol (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 21: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 22: Lab Notebook (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 23: Data for Formoterol High Dose (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 24: Stability Study for Formoterol Fumarate Inhalation Solution 20 mcg/2mL (Sepracor) [Dey Confidential—Filed Under Seal].
- Opening Expert Report of Robert Williams III Exhibit 40: Declaration of P. Banerjee dated Sep. 24, 2004 submitted in U.S. Appl. No. 09/887,496 (Dey).

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Opening Expert Report of Robert Williams III Exhibit 41: Table Supporting Declaration of P. Banerjee dated Sep. 24, 2004 submitted in U.S. Appl. No. 09/887,496 (Dey).
 Opening Expert Report of Robert Williams III Exhibit 42: Listing of Documents Reviewed.
 Opening Expert Report of Robert Williams III Exhibit 43: Lab Notebook [Dey Confidential—Filed Under Seal].
 Opening Expert Report of Robert Williams III Exhibit 44: Lab Notebook [Dey Confidential—Filed Under Seal].
 Opening Expert Report of Robert Williams III Exhibit 45: Method Qualification Results (Murakami and Gao) (Dey).
 Reply Expert Report of Robert Williams III, Nov. 20, 2009 [Dey Confidential—Filed Under Seal] [Sepracor Confidential—Redacted].
 Reply Expert Report of Robert Williams III Exhibit 46: Method Validation Report for HPLC Assay of Formoterol Fumarate and its Related Substances in Formoterol Fumarate Inhalation Solution, 20 mcg/2mL (ATM-716-13) (Sepracor) [Dey Confidential—Filed Under Seal].
 Reply Expert Report of Robert Williams III Exhibit 50: Study table (Sepracor) [Dey Confidential—Filed Under Seal].
 Reply Expert Report of Robert Williams III Exhibit 51: Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL (Sepracor) [Dey Confidential—Filed Under Seal].
 Reply Expert Report of Robert Williams III Exhibit 52: U.S. Patent No. 6,150,418 (provided as Document A93).
 Reply Expert Report of Robert Williams III Exhibit 55: Listing of Additional Documents Reviewed.
 Akapo Deposition Transcript, Nov. 10, 2008 (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 51: Personal Action Form (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 52: Employee Self Appraisal (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 53: U.S. Appl. No. 60/284,606.
 Akapo Deposition Exhibit 54: U.S. Patent No. 6,667,344 w/Partial File History.
 Akapo Deposition Exhibit 55: U.S. Patent No. 6,814,953 w/Partial File History.
 Akapo Deposition Exhibit 56: U.S. Patent No. 7,348,362 w/Partial File History.
 Akapo Deposition Exhibit 57: United States Code, Title 18, §§ 1001 to 1200.
 Akapo Deposition Exhibit 58: S. Akapo Award for the Performer Patents (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 59: A Comparative Stability Study Of Formoterol In Active Substance Concentrate (US Patent #6,150,418) and Dey's Formoterol Fumarate Inhalation Solutions (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 60: U.S. Patent No. 6,150,418 (provided as Document A93).
 Akapo Deposition Exhibit 61: Summary of Formoterol work done by M. Joyce (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 62: Summary of Stability Study for Formoterol Fumarate Inhalation Placebo (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 63: A stability-indicating HPLC assay method for formoterol and its related substances in formoterol fumarate dihydrate drug substance (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 64: Heat Degradation Study of Formoterol Inhalation Solution (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 65: Oral Inhalation PDT Meeting Minutes From Apr. 16, 2003 (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 66: Akapo, S., et al., *Validation of a RP-HPLC method for the assay of formoterol and its related substances in formoterol fumarate dihydrate drug substance*. J. Pharm. Biomed. Anal. 33 (2003) 935–945.
 Akapo Deposition Exhibit 67: Shelf Life Projection For Formoterol Fumarate Inhalation Solutions (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 68: E-mail (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 69: E-mail (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 70: E-mail (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 71: Formoterol PDT Meeting Minutes From Jan. 12, 2005 (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 72: Analytical Procedures (Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL) (Dey) [Dey Confidential—Filed Under Seal].
 Akapo Deposition Exhibit 73: Method Validation Report for HPLC Assay of Formoterol Fumarate and its Related Substances in Formoterol Fumarate Inhalation Solution, 20 mcg/2mL (ATM-716-13) (Dey) [Dey Confidential—Filed Under Seal].
 First Banerjee Deposition Transcript, Feb. 13, 2009 (Dey) [Dey Confidential—Filed Under Seal].
 First Banerjee Deposition Exhibit 118: Banerjee et al., *Studies on the Effect of Some Additives on the Stability of Injectable Formulations of Diazepam*, Indian Drugs 29 (8), 361–364 (May 1992).
 First Banerjee Deposition Exhibit 119: Letter from Banerjee to Patent Counsel with references (Dey) [Dey Confidential—Filed Under Seal].
 First Banerjee Deposition Exhibit 119[A]: Faulds, D., et al., *Formoterol A Review of its Pharmacological Properties and Therapeutic Potential in Reversible Obstructive Airways Disease*. Drugs 42 (1) pp. 115–137 1991.
 First Banerjee Deposition Exhibit 119[B]: Maesen, F.P.V., et al., *Formoterol Suspension Aerosol Comparison with Formoterol Solution Aerosol for 12 Weeks in Asthmatic Patients*. Chest 102:1544–1549 (1992) (provided as Document C45).
 First Banerjee Deposition Exhibit 119[C]: U.S. Patent No. 6,004,537 (provided as Document A82).
 First Banerjee Deposition Exhibit 119[D]: Anderson, G.P., *Formoterol: Pharmacology, molecular basis of Agorism, and mechanism of long duration of a highly potent and selective β_2 -adrenoceptor agonist bronchodilator*. Life Sciences, vol. 52, No. 26 pp. 2145–2160 (1993).
 First Banerjee Deposition Exhibit 119[E]: Rartow, R.A., et al., *Formoterol An Update of its Pharmacological Properties and Therapeutic Efficacy in the Management of Asthma*. Drugs, 55 (2) pp. 303–322 (Feb. 1998). (provided as Document C2).
 First Banerjee Deposition Exhibit 119[F]: PCT Publication WO 99/36095 (provided as Document B34).
 First Banerjee Deposition Exhibit 119[G]: PCT Publication WO 99/00134 (provided as Document B30).

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First Banerjee Deposition Exhibit 120: File History U.S. Patent No. 6,667,334.

First Banerjee Deposition Exhibit 121: Dey Product Development Monthly Report—Apr. 1999 (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Exhibit 122: Dey Product Development Monthly Report—Jun. 1999 (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Exhibit 123: Oral Inhalation PDT Meeting Minutes—Oct. 1999 (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Exhibit 124: Oral Inhalation PDT Meeting Minutes—Apr. 2000 (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Exhibit 125: Formoterol Fumarate Formulation Activities (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Exhibit 126: Dey Formulation Composition (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Exhibit 127: E-mail patent reminder (Dey) [Dey Confidential—Filed Under Seal].

First Banerjee Deposition Exhibit 128: U.S. Patent No. 7,462,645 (provided as Document A137).

First Banerjee Deposition Exhibit 129: U.S. Patent No. 7,473,710 (provided as Document A139).

First Banerjee Deposition Exhibit 130: U.S. Patent No. 7,465,756 (provided as Document A138).

Second Banerjee Deposition Transcript, Sep. 15, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Second Banerjee Deposition Exhibit 180: Personnel Action Form (Dey) [Dey Confidential—Filed Under Seal].

Second Banerjee Deposition Exhibit 181: Correspondence between Dey and Patent Counsel (Dey) [Dey Confidential—Filed Under Seal].

Second Banerjee Deposition Exhibit 182: Declaration of P. Banerjee dated Sep. 24, 2004 submitted in U.S. Appl. No. 09/887,496.

Second Banerjee Deposition Exhibit 183: Lab Notebook (Dey) [Dey Confidential—Filed Under Seal].

Second Banerjee Deposition Exhibit 184: Formoterol Fumarate Nebulization U.D.—For the treatment of COPD (Dey) [Dey Confidential—Filed Under Seal].

Second Banerjee Deposition Exhibit 185: Citations from Biological Abstracts (Dey) [Dey Confidential—Filed Under Seal].

Second Banerjee Deposition Exhibit 186: Converted concentrations from Formoterol fumarate to Formoterol free base. (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Transcript, Feb. 5, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 99: Dey Scientific Affairs Track record Jan. 2004–Aug. 2007 (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 100: Dey to Center for Drug Research—Change of Correspondence (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 101: Minutes from Apr. 23, 2003 NPC Meeting (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 102: Application To Market A New Drug, Biologic, Or An Antibiotic Drug For Human Use (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 103: E-mail Transmitting Formoterol Patent Opinion (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 104: Letter to FDA Formoterol Fumarate Inhalation Solution, 20 mcg/mL—Petition To Correct Patent Information (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 105: Letter to FDA Performist™ (formoterol fumarate) Inhalation Solution 20 mcg/2 mL Submission of Patent Information (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 106: PDT Update Sep. 23, 2004 (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 107: Formoterol PDT Meeting Minutes From Oct. 13, 2004 (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 108: Chronology Regulatory & Clinical Activities Formoterol Fumarate (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 109: Formoterol—Quality 5% desformyl degradant (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 110: EOP2 FDA Meeting Action Plan (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 111: Memorandum of Meeting Minutes with FDA on May 13, 2003 (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 112: Formoterol PDT Meeting Minutes From Sep. 8, 2004 (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 113: Formoterol Uni Dose for COPD (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 114: Formoterol Pls (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 115: Oral Inhalation PDT Meeting Minutes From Jul. 10, 2002 (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 116: Oral Inhalation PDT Meeting Minutes From Nov. 13, 2002 (Dey) [Dey Confidential—Filed Under Seal].

Carpenter Deposition Exhibit 117: Letter from Dey to FDA Formoterol Fumarate Inhalation Solution, 20 mcg/2 ML Minor Amendment—Patent Certification Amendment (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Transcript, Jun. 30, 2009 (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 142: Deposition of I. Chaudry in Dey v. Ivax Pharmaceuticals in the United States District Court for the Central District of California, Civil Action No. SACV 04-00079 (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 143: Letter between litigation counsel regarding discovery (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 144: Correspondence between Dey and Patent Counsel (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 145: Stability of Formoterol Fumarate in Purified Water (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 146: Dey Invention Award Plan (Dey) [Dey Confidential—Filed Under Seal].

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First Chaudry Deposition Exhibit 147: Dey Inventor Incentive Award Calculations (Dey) [Dey Confidential—Filed Under Seal].

First Chaudry Deposition Exhibit 148: Formoterol Overview Stage II (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Transcript, Jul. 1, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 126A: Formulation Composition (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 149: Oral Inhalation PDT Meeting Minutes From Oct. 2000 (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 150: Stability and Expiration Dating of Formoterol (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 151: Letter regarding Formoterol U.D. (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 152: Merck Innovation Award (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 153: Sepracor's Rule 30(b)(6) Notice of Deposition in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 154: Sepracor's Third Rule 30(b)(6) Notice to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 155: I. Chaudry Employee Profile (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 156: Scientific Affairs MBO 2004 (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 157: Scientific Affairs MBO 2005 (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 158: Estimate of Nebulization Market Size (Dey) [Dey Confidential—Filed Under Seal].

Second Chaudry Deposition Exhibit 159: Formoterol Fumarate IS Solution pH (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Transcript, Jan. 30, 2009 (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 74: Dey Portfolio Presentation (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 75: E-mail regarding Formoterol Patent (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 76: Minutes from the NPC Meeting Day 2005 (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 77: Publication and Abstract Plan (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 78: Minutes from the Medical Advisors Meeting, May 2005 (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 79: 2004 R&D Plan and Project Prioritization (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 80: Presentation of Professor Schedule—Business Development Update (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 81: Performist Launch Delay Memo (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 82: Formoterol U.D. Memo (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 83: Timing in 20% Reduction in Sales Force (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 84: Dey Award Plan for Inventions (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 85: E-mail regarding Sepracor (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 86: Presentation of Dey Award for the Performist Patents (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 87: E-mail regarding out licensing (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 88: Co-promotion agreement with Dey and Critical Therapeutics (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 89: E-mail regarding 4-year impacts (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 90: Revised Plaintiff's Privileged Log (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 91: Senior Team Meeting Minutes (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 92: E-mail for "formoterol disaster" (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 93: Dey Net Sales Projection (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 94: Pipeline Activity Summary (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 95: Antwort Respiratory Strategy (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 96: Net Sales Report (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 97: Performist Net Sales (Dey) [Dey Confidential—Filed Under Seal].

First Engle Deposition Exhibit 98: North America Mgt Presentation—Pipeline Page (Dey) [Dey Confidential—Filed Under Seal].

Second Engle Deposition Transcript, Sep. 16, 2009 [Dey Confidential—Filed Under Seal].

Glascott Deposition Transcript, Aug. 13, 2009 [(Dey) Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG1: Sepracor's Second Rule 30(b)(6) Notice to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353, Mar. 21, 2007 [Pam Marrs 1] [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG2: Press Release Mylan's Dey L.P. Announces Establishment of 'J-Code' for Performist™ Inhalation Solution.

Glascott Deposition Exhibit VG3: Draft Updated Medical Policy for Medicare and Medicaid (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG4: Bates Ranges (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG5: Letter to TrustSolutions with additional regarding Performist™ (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG6: Borde, M., *Treatment Algorithms for Chronic Obstructive Pulmonary Disease*, Dec. 2006, Decision Resources, 2006 (Dey) [Dey Confidential—Filed Under Seal].

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Glascott Deposition Exhibit VG7: Monie, D., *Chronic Obstructive Pulmonary Disease Treatment & Reimbursement—Findings from a U.S. Survey of PCPs, Pulmonologist, and Managed Care Pharmacy Directors*. Decision Resources, Nov. 2006 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG8: Review of Dey Sales Projections (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG9: Situational Analysis of Chronic Obstructive Pulmonary Disease (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG10: US Formoterol Market Overview, Mar. 2002 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG11: Unit Dose Opportunity Assessment (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG12: Marketing Definition Memo (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG13: New Market Definitions (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG14: Price per day Comparison on WAC (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG15: Formoterol Launch Forecast (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG16: Perforomist™ Projections (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG17: Perforomist™ Retail Price Summary (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG18: E-mail regarding Perforomist™ Launch Offer Recco (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG19: Pricing Recommendation for Perforomist™ Inhalation Solution (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG20: Branded Pipeline Forecast by Indication and Segment (Dey) [Dey Confidential—Filed Under Seal] [Pam Marrs 30].

Glascott Deposition Exhibit VG21: E-mail regarding discussion with Bankers (Dey) [Dey Confidential—Filed Under Seal] [Pam Marrs 27].

Glascott Deposition Exhibit VG22: Formoterol Lost Profits (Dey) [Dey Confidential—Filed Under Seal] [Pam Marrs 23].

Glascott Deposition Exhibit VG23: Optimal Bronchodilation in COPD: Making a Long Story Short (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG24: E-mail FFIS Field Strategy (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG25: E-mail Retention and Maintenance C27100 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG26: E-mail *DuoNeb* vs. *Brovana* Sales aid (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG27: Formoterol Competitive Workshop (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG28: Brovana War Games Summary (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG29: Dey Formoterol Forecast Compared to Arformoterol forecast (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG30: Perforomist Message to Internal and External Customers (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG31: E-mail on Back-orders (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG32: Marketing Department Org Chart (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG33: Formoterol Launch Plan Update (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG34: Formoterol Transition Plan (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG35: Formoterol Launch Commercialization Team (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG36: Formoterol Update (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG37: FFIS Launch Commercialization Meeting Jan. 10, 2007 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG38: FFIS Launch Commercialization Meeting Feb. 1, 2007 (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG39: Perforomist™ National Sales Plan (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG40: 2008 Perforomist™ Inhalation Solution Launch Marketing Plan (Dey) [Dey Confidential—Filed Under Seal].

Glascott Deposition Exhibit VG41: 2008 Perforomist™ Inhalation Solution Launch Marketing Plan (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Transcript, Aug. 11, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX165: Updated Summary of Formoterol PAI Preparation Meetings (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX166: Stability Data for Formoterol Fumarate Inhalation Solution, 20 mcg/2mL (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX167: Finished Product Methods Requiring Transfer Qualifications (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX168: HPLC Assay of Formoterol Fumarate and its Related Substances in Formoterol Fumarate Inhalation Solution (20 mcg/2mL and 20 mcg/0.5 mL) (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX 169: Stability Study Protocol for Dey's Perforomist™ (Formoterol Fumarate) Inhalation Solution Against Sepracor's Brovana™ (Arformoterol Tartrate) Inhalation Solution (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX170: Analytical Development Test Request for Brovana™ (Arformoterol Tartrate) Inhalation Solution, 15 mcg/2 mL (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX171: Analytical Development Test Request for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX172: Analytical Development Test Request for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL—1 month @ 25±2° C./60±5 %RH (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX173: Analytical Development Test Request for Brovana™ (Arformoterol Tartrate) Inhalation Solution, 15 mcg/2 mL—1 month @ 25±2° C./60±5 %RH (Dey) [Dey Confidential—Filed Under Seal].

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Gupta Deposition Exhibit DX174: Analytical Development Test Request for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL—2 months @ $25 \pm 2^\circ \text{C}$ /60 \pm 5%RH (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX175: Analytical Development Test Request for Brovana™ (Arformoterol Tartrate) Inhalation Solution, 15 mcg/2 mL—2 months @ $25 \pm 2^\circ \text{C}$. 60 \pm 5 %RH (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX176: Lab Notebook (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX177: Lab Notebook (Dey) [Dey Confidential—Filed Under Seal].

Gupta Deposition Exhibit DX178: Akapo, et al. *Evaluation of Interconversion of (RR)- and (SS)-Enantiomers in Perforomist™ (Formoterol Fumarate and Brovana™ (Arformoterol Tartrate) Inhalation Solutions* (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Transcript, Sep. 5, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX1: Serpacor's Rule 30(b)(6) Notice of Deposition of Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York; Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX2: Dey's Initial Disclosure in *Dey v. Sepracor* in the United States District Court of the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX3: Sepracor's First Set of Requests for the Production of Documents to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX4: Sepracor's Second Set of Requests for the Production of Documents to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX5: Sepracor's Third Set of Request for the Production of Document to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX6: Subpoena of Heller Ehman in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Jones Deposition Exhibit DX7: Revised Agreement for Electronic Discovery in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Kling Deposition Transcript, Aug. 20, 2009 (No Exhibits) (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Transcript, Sep. 11, 2008 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX34: Orange Book Detail Search for Formoterol Fumarate.

Laskar Deposition Exhibit DX35: NDA Description and Composition of the Drug Product (Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX36: Oral Inhalation PDT Meeting Minutes From Jul. 9, 2003 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX37: Oral Inhalation PDT Meeting Minutes From Feb. 11, 2004 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX38: Pharmaceutical Development MBOs (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX39: Date of the formulation of the 10 mcg/mL composition. (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX40: Ayres, J, et al., *Student Experiments in Pharmaceutical I.V. Additives, Chemical Incompatibilities, Kinetics, And The Arrhenius Equation*. American Journal of Pharmaceutical Education, Student Experiments in Pharmaceutics, pp. 58–68.

Laskar Deposition Exhibit DX41: Laskar, P., et al., *Degradation of Carmustine in Aqueous Media*. *Journal of Pharmaceutical Sciences*, vol. 66, No. 8, pp. 1073–1076, Aug. 1977.

Laskar Deposition Exhibit DX42: U.S. Patent Publication 2005/0009836.

Laskar Deposition Exhibit DX43: PCT Publication WO 93/20796.

Laskar Deposition Exhibit DX44: Pharmaceutical Development Report Formoterol Fumarate Inhalation Solution 20 mcg/2 mL (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX45: U.S. Patent No. 6,161,536 (provided as Document A95).

Laskar Deposition Exhibit DX46: Formoterol PDT Meeting Minutes From May 11, 2005 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX47: Draft Minutes from the NPC Meeting held Jul. 19, 2005 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX48: Pharmaceutical Development MBOs 2005 (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX49: Dey Innovation Note (Dey) [Dey Confidential—Filed Under Seal].

Laskar Deposition Exhibit DX50: Edits/Questions for Pharm/Tox Sections (Dey) [Dey Confidential—Filed Under Seal].

Lee Deposition Transcript, Jul. 14, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Lee Deposition Exhibit DX160: *Ex Parte* Reexamination Request for U.S. Patent No. 6,667,344 (Copy not submitted, see Reexamination U.S. Appl. No. 90/010,488).

Lee Deposition Exhibit DX161: *Ex Parte* Reexamination Request for U.S. Patent No. 6,814,953 (Copy not submitted; see Reexamination U.S. Appl. No. 90/010,489).

Lee Deposition Exhibit DX162: Privilege Log (Dey) [Dey Confidential—Filed Under Seal].

Lee Deposition Exhibit DX163: Order Granting *Ex Parte* Reexamination Request for U.S. Patent No. 6,667,344 (Copy not submitted, see Reexamination U.S. Appl. No. 90/010,488).

Lee Deposition Exhibit DX164: Order Granting *Ex Parte* Reexamination Request for U.S. Patent No. 6,814,953 (Copy not submitted; see Reexamination U.S. Appl. No. 90/010,489).

First Marrs Deposition Transcript, Aug. 12, 2009 (Dey) [Dey Confidential—Filed Under Seal].

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First Marrs Deposition Exhibit PM1: Sepracor's Second Rule 30(b)(6) Notice to Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM2: Dey's Supplemental Objections And Responses To Sepracor's First Set Of Interrogatories To Dey in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM3: Dey Net Sales Perforomist (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM4: Dey Performist 2008 Actual (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM5: Dey Performist 2009 Actual (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM6: 2007 Key Indicator Graphs (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM7: Formoterol UD NDA Communication (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM8: Investment Committee Meeting (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM9: Capital Request for Molds (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM10: E-mail regarding vial design (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM11: Performist Inventory on Hand (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM12: E-mail on Back-orders (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM13: Message to the Senior Team (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM14: Summary of Net Sales Changes 2007 & 2008 (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM15: Impact on Formoterol (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM16: Various Projections in 2015 Scenarios (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM17: Dey Amendment No. 3 to Form S-1 Registration Statement.

First Marrs Deposition Exhibit PM18: E-mail regarding Formoterol Forward (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM19: Orange Book Detail Search for Arbuterol Sulfate.

First Marrs Deposition Exhibit PM20: U.S. Patent No. 6,632,842 (provided as Document A128).

First Marrs Deposition Exhibit PM21: HIP Analysis (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM22: Formoterol Forecast based on Launch Dates (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM23: Formoterol Lost Profits (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM24: Formoterol Increased sales from early launch of 2 ml vs lost LV Sales (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM25: Formoterol Oct. 2007 Launch Sales (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM26: Formoterol Low Volume Discontinuance (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM27: E-mail regarding discussion with Bankers (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM28: E-mail regarding conversation with bankers, extended (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM29: E-mail regarding "beta-agonist" (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM30: Branded Pipeline Forecast by Indication and Segment (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM31: Branded Budgeted Development Projects (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM32: Dey Sales Revised 4 Year Plan (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM33: Dey P&L Summary (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM34: Formoterol P&L to 2011 (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM35: Market Share Forecast (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM36: Patent Share Chart (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM37: Dey sales by Product (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM38: Dey Sales & Margin Before CAMS (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM39: Dey 2008 Budget (Dey) [Dey Confidential—Filed Under Seal].

First Marrs Deposition Exhibit PM40: Dey 2007 Strategic Plan (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Transcript, Sep. 24, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM41: Dey Sales All Products (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM42: 2008 Product Line P&L Analysis vol. 1 Actual (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM43: 2008 Product Line P&L Analysis vol. 2 Actual (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM44: Dey Gross to Net Sales (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM45: Fixed Assets Acquired Specifically for Performist (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM46: Performist Rebate for Neighborhood Health Plan (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM47: Performist Rebate for Beyond Rx (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM48: Contract Renewal for Virtua Health (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM49: FFDIS Developing a US Pricing and Market Access Strategy (Dey) [Dey Confidential—Filed Under Seal].

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Second Marrs Deposition Exhibit PM50: Perforomist™ Miscellaneous Correspondance (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM51: New Market Definitions (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM52: E-mail on FFIS Pre-appr Field Strategy (Dey) [Dey Confidential—Filed Under Seal].

Second Marrs Deposition Exhibit PM53: Branded Pipeline Forecasts by Indication and Segment (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Transcript, Sep. 23, 2009 (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Exhibit 131: U.S. Patent No. 7,541,385 (provided as Document A140).

Mercanti Deposition Exhibit 132: Declaration of Michael N. Mercanti, Esq. in Support of Dey's Opposition to Sepracor's Motion for Leave to File an Amended Answer and Counterclaims in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Exhibit 133: Dey's Supplemental Objections And Response To Sepracor's First Set Of Interrogatories To Dey (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Exhibit 134: U.S. Patent No. 7,462,645 and partial File History.

Mercanti Deposition Exhibit 135: U.S. Patent No. 7,473,710 and partial File History.

Mercanti Deposition Exhibit 136: U.S. Patent No. 7,465,756 and partial File History.

Mercanti Deposition Exhibit 137: U.S. Patent No. 7,541,385 and partial File History.

Mercanti Deposition Exhibit 138: Partial File History U.S. Appl. No. 09/887,496.

Mercanti Deposition Exhibit 139: Final Office Action mailed May 26, 2009 in U.S. Appl. No. 10/145,978.

Mercanti Deposition Exhibit 140: Privileged Log (Dey) [Dey Confidential—Filed Under Seal].

Mercanti Deposition Exhibit 141: Sepracor's Answer And Counterclaims To Dey's Second Supplemental Complaint in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-2353 (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Transcript, Sep. 9, 2008 (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX08: U.S. Patent No. 6,677,344 (provided as Document A129).

Pham Deposition Exhibit DX09: U.S. Patent No. 6,814,953 (provided as Document A133).

Pham Deposition Exhibit DX10: U.S. Patent No. 7,348,362 (provided as Document A136).

Pham Deposition Exhibit DX11: Project Assignment For Unit Dose Scientists (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX12: Declaration and Power of Attorney for U.S. Appl. No. 09/887,281.

Pham Deposition Exhibit DX13: Formoterol Fumarate Inhalation Solution 20 mcg/2 L Original NDA (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX14: Formoterol Fumarate Inhalation Solution Clinical Batches (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX15: Formulation Selection Memo (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX16: Pharmaceutical Development MBOs (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX17: Formoterol Solubility and pH Stability Profile (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX18: U.S. Patent No. 6,040,344 (provided as Document A85).

Pham Deposition Exhibit DX19: Petitions to Correct Inventorship in Patent No. 6,667,344.

Pham Deposition Exhibit DX20: Petitions to Correct Inventorship in Patent No. 6,814,953.

Pham Deposition Exhibit DX21: Application for U.S. Patent No. 7,348,362.

Pham Deposition Exhibit DX22: Petitions to Correct Inventorship in U.S. Appl. No. 10/887,785.

Pham Deposition Exhibit DX23: Formoterol Updates (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX24: Maesen, F.P., et al., *Formoterol suspension aerosol, Comparison with formoterol solution aerosol for 12 weeks in asthmatic patients*. Chest 102:1544–1549 (1992) (provided as Document C45).

Pham Deposition Exhibit DX25: Merck Innovation Award (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX26: Preliminary Stability Assessment Of Formoterol Fumarate in Aqueous Solution (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX27: Formulation Development of Formoterol Inhalation Unit Dose (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX28: Summary of Formoterol Unit Dose Formulation Development (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX29: Formulation Selection Justification Report (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX30: Formoterol Unit Dose—Timeline and Key Milestones (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX31: Letter to D. Rieger (Dey) [Dey Confidential—Filed Under Seal].

Pham Deposition Exhibit DX32: U.S. Patent No. 3,994,974 (provided as Document A23).

Pham Deposition Exhibit DX33: Response to Final Office Action, mailed Apr. 22, 2003 in U.S. Appl. No. 09/887,281.

Rieger Deposition Exhibit DX179: Feb. 25, 2003 Fax Transmission from Partha S. Banerjee to Dale L. Rieger, Ph.D.; Composition of Formoterol Clinical Formulation (Dey) [Dey Confidential—Filed Under Seal].

A Comparative Stability Study Of Formoterol In Active Substance Concentrate (US Patent #6,150,418 [to Hochrainer et al.]) and Dey's Formoterol Fumarate Inhalation Solutions Oct. 10, 2005.

Stenesh, J., *Dictionary of Biochemistry and Molecular Biology* (2d ed. 1989), p. 364.

Sterns, R.H. et al., *Salt and water: read the package insert*, Q. J. Med. (2003), 96:549–552.

Bates, R. et al., *Standards for pH Measurements in Isotonic Saline Media of Ionic Strength I=0.16*, Analytical Chemistry (vol. 50, No. 9, Aug. 1978), 1295–1300.

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- Roy, R. et al., *Buffer Standards for the Physiological pH of Zwitterionic Compounds, MOBS and TABS from 5 to 55° C.*, J. Solution Chemistry (vol. 33, No. 10, Oct. 2004), pp. 1199–1211.
- Docket Sheet dated Apr. 5, 2011 in *Dey v. Sepracor* in the United States District Court for the Southern District of New York, Civil Action No. 1:07-cv-02353-JGK-RLE, Mar. 21, 2007.
- Docket Sheet dated Apr. 5, 2011 in *Dey v. Teva* in United States District Court for the Northern District of West Virginia, Civil Action No. 1:09-cv-00087-IMK, Jun. 23, 2009.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit dated Oct. 1, 2010 in *Dey v. Teva* in the United States District Court for the Northern District of West Virginia, Civil Action No. 1:09-cv-00087-IMK, Jun. 23, 2009.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit A: U.S. Patent No. 6,667,344.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit B: U.S. Patent No. 6,814,953.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit C: U.S. Patent No. 7,348,362.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit D: U.S. Patent No. 7,462,645.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit E (6 parts): Excerpts from the Reexamination Files of the '344 Patent (Reexamination No. 90/010,488) and the '953 Patent (Reexamination No. 90/010,489).
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit F (4 parts): Excerpts from the File History of U.S. Appl. No. 09/887,281.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit G (8 parts): Excerpts from the File History of U.S. Appl. No. 10/138,866.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit H (6 parts): Excerpts from the File History of U.S. Appl. No. 10/887,785.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit I (4 parts): Excerpts from the File History of U.S. Appl. No. 11/688,429.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit J: Claim Chart.
- Defendant Teva's Opening Memorandum in Support of Its Claim Construction of the Patents-in-Suit, Exhibit K: Parties' Agreed Claim Constructions.
- Dey's Memorandum in Support of their Claim Construction (and Exhibits 1–22) dated Oct. 1, 2010 in *Dey v. Teva* in the United States District Court for the Northern District of West Virginia, Civil Action No. 1:09-cv-00087-IMK, Jun. 23, 2009.
- Teva's Rebuttal Memorandum on the Issue of Claim Construction of the Patents-in-Suit dated Oct. 15, 2010.
- Dey's Rebuttal Claim Construction Report (and Exhibits 23–24) dated Oct. 15, 2010.
- Expert Report of Dr. Gordon Rausser Footnote 52: Chronic bronchitis and emphysema prevalence in U.S. adults (age 18 and older), 1999–2008.
- Expert Report of Dr. Gordon Rausser Footnote 52: Estimated lifetime asthma diagnosis prevalence in children and adults in the US 1997–2008 (0–17 yrs).
- Expert Report of Dr. Gordon Rausser Footnote 31: Connolly et al., *Inhaler Technique of Elderly Patients: Comparison of Metered-dose Inhalers and Large Volume Spacer Devices*, Age and Ageing (vol. 24, No. 3, 1995), pp. 190–192.
- Expert Report of Dr. Gordon Rausser Footnote 29: Armitage, J.M. et al., *Inhaler Technique in the Elderly*, Age and Ageing (vol. 17, No. 4, 1988), pp. 275–278.
- Expert Report of Dr. Gordon Rausser Footnote 43: Boe, J. et al., *European Respiratory Society Guidelines on the use of nebulizers*, Eur. Respir. J. (vol. 18, 2001), pp. 228–242.
- Expert Report of Dr. Gordon Rausser Footnote 28: Labrune, S. et al., *Inhaled therapy in asthma: Metered-dose inhaler experience*, Monaldi Arch. Chest Dis. (vol. 49, No. 3, 1994), pp. 254–257.
- Expert Report of Dr. Gordon Rausser Footnote 40: *Perforomist Inhalation Solution Data Presented At American Thoracic Society Conference*, Medical News Today (May 20, 2009) (located at <http://www.medicalnewstoday.com/articles/150812.php>).
- Expert Report of Dr. Gordon Rausser Footnote 27: Schmidt, D. et al., *Effect of enantiomers of formoterol on inherent and induced tone in guinea-pig trachea and human bronchus*, Naunyn-Schmiedeberg's Arch. Pharmacol. (vol. 261, 2000), pp. 405–409.
- Expert Report of Dr. Gordon Rausser Footnote 4: Seemungal T. et al., *Time Course and Recovery of Exacerbations in Patients with Chronic Obstructive Pulmonary Disease*, Am. J. Respir. Crit. Care Med. 161:1608–1613 (2000).
- Expert Report of Leslie Hendeles Exhibit 17: Beasley, R. et al., *Preservatives in Nebulizer Solutions: Risks without Benefit—A Further Comment*, Pharmacotherapy (vol. 19, No. 4, 1999), pp. 473–474.
- Expert Report of Leslie Hendeles Exhibit 18: *Sterility Requirements for Inhalation Solution Products*, 62 Fed. Reg. 49,638 (Sep. 23, 1997).
- Expert Report of Leslie Hendeles Exhibit 19: *Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation*, 65 Fed. Reg. 34,082 (May 26, 2000).
- Expert Report of Leslie Hendeles Exhibit 20: U.S. Dept. Health & Human Services, *Approved Drug Products with Therapeutics Equivalence Evaluations*, (13th ed., 1993) p. 3–7.
- Expert Report of Leslie Hendeles Exhibit 21: *Physicians' Desk Reference* (47th ed., 1993), pp. 582–585.
- Expert Report of Leslie Hendeles Exhibit 22: *Physicians' Desk Reference* (52d ed., 1998), pp. 2657–2659.
- Expert Report of Leslie Hendeles Exhibit 23: *Physicians' Desk Reference* (52d ed., 1998), pp. 1556–1557.
- Expert Report of Leslie Hendeles Exhibit 24: File History for Accuneb Trademark Application Serial No. 75/615,399.
- Expert Report of Leslie Hendeles Exhibit 26: *Prescribing Information for Pulmicort Respules™ (budesonide inhalation suspension) 0.25 mg and 0.5 mg* (revised Aug. 4, 2000).
- Expert Report of Leslie Hendeles Exhibit 27: *Physicians' Desk Reference* (54th ed., 2000), pp. 2316–2318.
- Expert Report of Leslie Hendeles Exhibit 29: *Physicians' Desk Reference* (52d ed., 1998), pp. 702–704.

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- Expert Report of Leslie Hendeles Exhibit 30: *Physicians' Desk Reference* (52d ed., 1998), p. 560.
- Expert Report of Leslie Hendeles Exhibit 31: *Physicians' Desk Reference* (52d ed., 1998), pp. 2368-2369.
- Expert Report of Leslie Hendeles Exhibit 32: Boehringer Ingelheim Pharmaceuticals, Inc., *Prescribing Information for Atroven®* (revised Oct. 1998).
- Expert Report of Leslie Hendeles Exhibit 42: Hendeles et al., *Dose-response Of Inhaled Diltiazem On Airway Reactivity To Methacholine And Exercise In Subjects With Mild Asthma*, Clin. Pharmacol. Ther. (vol. 43, Apr. 1988), pp. 387-392.
- Expert Report of Leslie Hendeles Exhibit 45: Lindberg et al., *The effects of formoterol, a long-acting β -adrenoceptor agonist, on mucociliary activity*, Eur. J. Pharmacology (vol. 285, No. 3, Oct. 24, 1995), pp. 275-280.
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**EX PARTE
REEXAMINATION CERTIFICATE
ISSUED UNDER 35 U.S.C. 307**

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in *italics* indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 1, 21-25, 38-42, 74, 94-98 and 111-115 are determined to be patentable as amended.

Claims 2-20, 26-37, 57-63, 75, 76, 77-93, 99-110, 120-124 and 130-136 dependent on an amended claim, are determined to be patentable.

New claims 147-163 are added and determined to be patentable.

Claims 43-56, 64-73, 116-119, 125-129 and 137-146 were not reexamined.

1. A kit, comprising:

(a) a pharmaceutical composition[,] comprising formoterol, or a derivative thereof, in a pharmacologically suitable [fluid] *aqueous solution*, wherein the composition is stable during long term storage, [the fluid comprises water,] and [the composition] is formulated at a concentration suitable for direct administration by nebulizer to a subject in need [thereof] of bronchodilation, without propellant and without dilution of the composition prior to administration; and

(b) a nebulizer.

21. The kit of claim 1, wherein the formoterol free base concentration in the composition is about 5 µg/mL to about [2 mg/mL] 50 µg/mL.

22. The kit of claim 21, wherein the formoterol free base concentration in the composition is about [10] 5 µg/mL to about [1 mg/mL] 10 µg/mL.

23. The kit of claim [22] 21, wherein the formoterol free base concentration in the composition is about [50] 10 µg/mL to about [200] 50 µg/mL.

24. The kit of claim [23] 1, wherein the formoterol free base concentration in the composition is about 59 µg/mL.

25. The kit of claim [23] 1, wherein the formoterol free base concentration in the composition is about 118 µg/mL.

38. The kit of claim 26, wherein the formoterol free base concentration in the composition is about 5 µg/mL to about [2 mg/mL] 50 µg/mL.

39. The kit of claim 28, wherein the formoterol free base concentration in the composition is about [10] 5 µg/mL to about [1 mg/mL] 50 µg/mL.

40. The kit of claim 39, wherein the formoterol free base concentration in the composition is about [50] 5 µg/mL to about [200] 10 µg/mL.

41. The kit of claim [40] 26, wherein the formoterol free base concentration in the composition is about 59 µg/mL.

42. The kit of claim [40] 26, wherein the formoterol free base concentration in the composition is about 118 µg/mL.

74. A method for the treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive

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disorders, comprising administering an effective amount of a pharmaceutical composition by nebulizer to a subject in need of such treatment, wherein the pharmaceutical composition comprises formoterol or a derivative thereof, formulated at a concentration suitable for direct administration to a subject in need [thereof] of bronchodilation, without propellant and without dilution of the composition prior to administration, wherein said formoterol or derivative is present in a pharmacologically suitable [fluid] *aqueous solution*, and wherein the composition is stable during long term storage [and the fluid comprises water].

94. The method of claim 74, wherein the formoterol free base concentration in the composition is about 5 µg/mL to about [2 mg/mL] 50 µg/mL.

95. The method of claim 94, wherein the formoterol free base concentration in the composition is about [10] 5 µg/mL to about [1 mg/mL] 10 µg/mL.

96. The method of claim [95] 94, wherein the formoterol free base concentration in the composition is about [50] 10 µg/mL to about [200] 50 µg/mL.

97. The method of claim [96] 74, wherein the formoterol free base concentration in the composition is about 59 µg/mL.

98. The method of claim [96] 74, wherein the formoterol free base concentration in the composition is about 118 µg/mL.

111. The method of claim 99, wherein the formoterol free base concentration in the composition is about 5 µg/mL to about [2 mg/mL] 50 µg/mL.

112. The method of claim 111, wherein the formoterol free base concentration in the composition is about [10] 5 µg/mL to about [1 mg/mL] 10 µg/mL.

113. The method of claim [112] 111, wherein the formoterol free base concentration in the composition is about [50] 10 µg/mL to about [200] 50 µg/mL.

114. The method of claim [113] 99, wherein the formoterol free base concentration in the composition is about 59 µg/mL.

115. The method of claim [113] 99, wherein the formoterol free base concentration in the composition is about 118 µg/mL.

147. A method for the treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, comprising

administering an effective amount of a pharmaceutical composition by nebulizer to a human subject in need of such treatment, wherein

the pharmaceutical composition is a sterile unit dosage form that is suitable for long term storage and comprises a pharmacologically suitable *aqueous saline solution*, a buffer, and formoterol or derivative thereof, said formoterol or derivative is present at a concentration corresponding to about 5 µg/mL to about 50 µg/mL of formoterol free base,

the composition has a pH of about 4.0 to about 6.0, and the composition is stable during long term storage.

148. A method according to claim 147, wherein said formoterol or derivative is present at a concentration corresponding to about 5 µg/mL to about 10 µg/mL of formoterol free base.

149. A method according to claim 147, wherein said formoterol or derivative is present at a concentration corresponding to about 10 µg/mL to about 50 µg/mL of formoterol free base.

150. A method of claim 148, wherein the pH is about 5.0.

151. A method of claim 150, wherein the composition is isotonic.

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152. A method of claim 147, wherein the formoterol or derivative thereof is a pharmacologically acceptable salt or hydrate of formoterol.

153. A method of claim 152, wherein said salt is one of a tartrate or a fumarate of formoterol.

154. A method of claim 147, wherein the formoterol or derivative thereof is formoterol fumarate dihydrate.

155. A method of claim 147, wherein the formoterol or derivative thereof is formoterol tartrate.

156. A method of claim 152, wherein said formoterol or derivative thereof is present as a mixture of enantiomers or stereoisomers.

157. A method of claim 152, wherein said formoterol or derivative thereof is present substantially as a single enantiomer or stereoisomer.

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158. A method of claim 157, wherein the single enantiomer or stereoisomer is 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide.

159. A method of claim 158, wherein said salt is one of a tartrate or a fumarate of formoterol.

160. A method of claim 156, wherein said salt is one of a tartrate or a fumarate of formoterol.

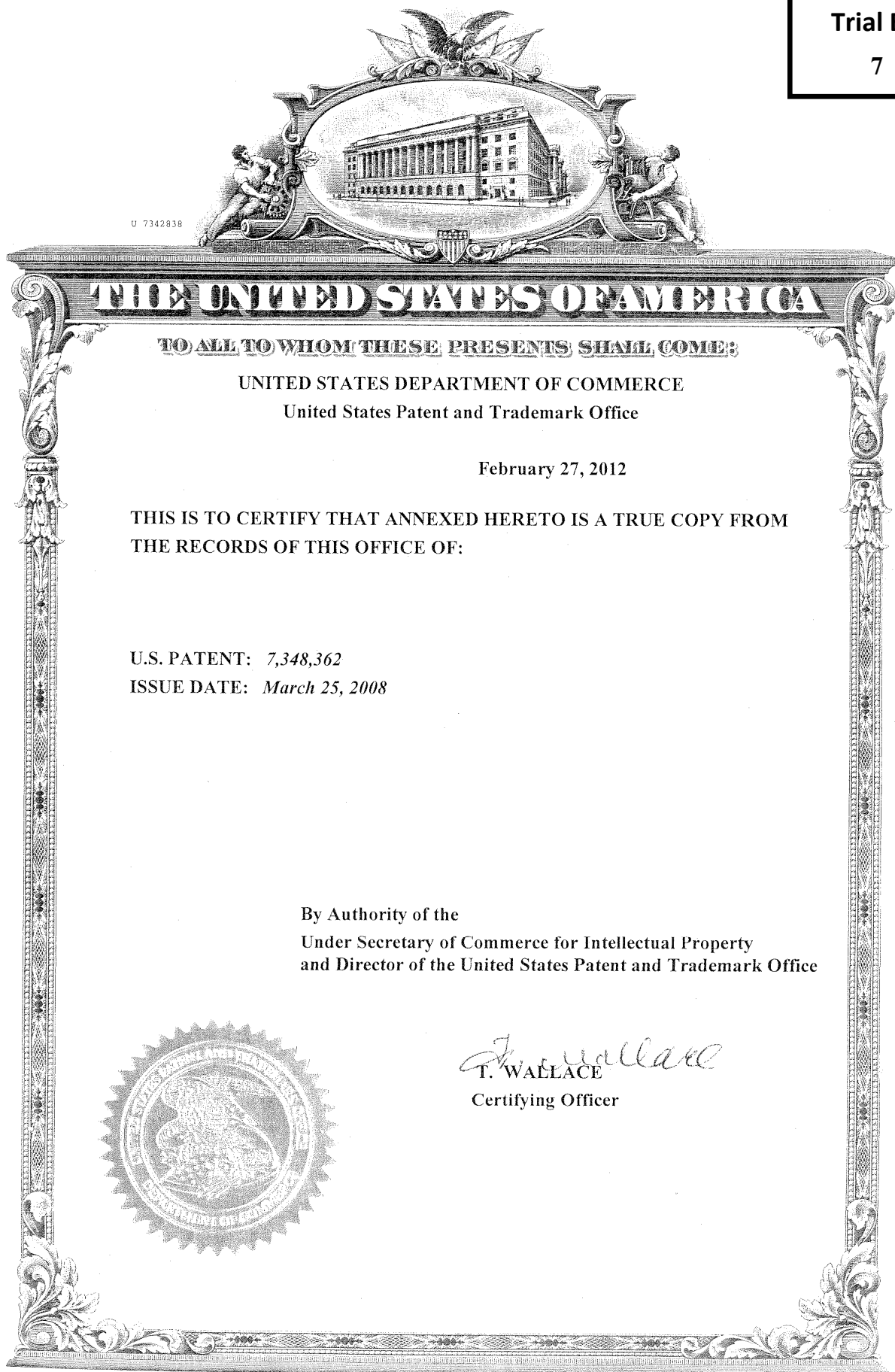
161. A method of claim 151, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

162. A method of claim 152, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

163. A method of claim 161, wherein the single unit dosage form comprises about 2 mL of said aqueous solution.

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US007348362B2

(12) **United States Patent**
Banerjee et al.

(10) **Patent No.:** **US 7,348,362 B2**
(45) **Date of Patent:** ***Mar. 25, 2008**

(54) **BRONCHODILATING β -AGONIST COMPOSITIONS AND METHODS**

(75) Inventors: **Partha S. Banerjee**, Wynnewood, PA (US); **Imtiaz A. Chaudry**, Napa, CA (US); **Stephen Pham**, Sacramento, CA (US)

(73) Assignee: **Dey, L.P.**, Napa, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 294 days.

This patent is subject to a terminal disclaimer.

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(22) Filed: **Jul. 9, 2004**

(65) **Prior Publication Data**

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(51) **Int. Cl.**
A61K 31/138 (2006.01)

(52) **U.S. Cl.** **514/651**

(58) **Field of Classification Search** None
See application file for complete search history.

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(74) *Attorney, Agent, or Firm*—Lucas & Mercanti, LLP

(57) **ABSTRACT**

Bronchodilating compositions and methods are provided. The compositions are intended for administration as a nebulized aerosol. In certain embodiments, the compositions contain formoterol, or a derivative thereof. Methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders using the compositions provided herein are also provided.

18 Claims, No Drawings

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BRONCHODILATING β -AGONIST COMPOSITIONS AND METHODS

RELATED APPLICATIONS

This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 60/486,386, filed Jul. 10, 2003, entitled "BRONCHODILATING β -AGONIST COMPOSITIONS AND METHODS." The disclosure of the above-referenced application is incorporated by reference herein in its entirety.

FIELD

Compositions and methods are provided relating to treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders. In particular, the compositions and methods herein include formoterol, and/or derivatives thereof. The compositions are propellant-free, sterile unit dose or multidose inhalation solutions intended for administration via nebulization.

BACKGROUND

Bronchoconstrictive disorders affect millions worldwide. Such disorders include asthma (including bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness), chronic bronchitis and other chronic obstructive pulmonary diseases. Compounds having β_2 -adrenoreceptor agonist activity have been developed to treat these conditions. Such compounds include, but are not limited to, Albuterol (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); Bambuterol (dimethylcarbamic acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenylene ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetrahydro-1-(3,4,5-trimethoxyphenyl)methyl)-6,7-isoquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Formoterol (2-hydroxy-5-(((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methyl-ethyl)amino)ethyl)formanilide); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methylethyl)amino)methyl)benzene-methanol); Hexoprenaline (4,4'-(1,6-hexanediy)l-bis(imino(1-hydroxy-2,1-ethanediy)l))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(2-pyridinyl)ethoxy)hexyl)amino)methyl)benzenemethanol); Pirbuterol (α^6 -(((1,1-dimethylethyl)amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol ((R*,S*)-(\pm)-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolinone); Reproterol ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)amino)methyl)-1,

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3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-(((1R)-1-hydroxy-2-(N-(((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)carbostyryl hydrochloride).

These compounds are typically formulated for inhalation therapy. Aqueous or liquid formulations are preferred over solid formulations. Powdered formulations are more difficult to administer, particularly to the young and elderly who are most often the patients in need of such therapy. Compounds, such as formoterol are not adequately stable in aqueous solutions to be formulated as liquids. Hence there is a need for formulations of compounds, such as formoterol, in a form that can be conveniently administered and that are stable for extended periods of time.

SUMMARY

Compositions and methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders are provided. The compositions provided herein are stable solutions of a bronchodilating agent, or a derivative thereof, in a pharmacologically suitable fluid that contains water, that are stable during long term storage. The compositions are suitable for direct administration to a subject in need thereof. Pharmacologically suitable fluids include, but are not limited to, polar fluids, including protic fluids. In certain embodiments herein, the compositions are aqueous solutions.

The compositions provided herein possess an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C. and greater than or equal to 1, 2 or 3 years storage time at 5° C. In certain of these embodiments, using Arrhenius kinetics, >80% or >85% or >90% or >95% estimated bronchodilating agent remains after such storage. These compositions are particularly useful for administration via nebulization. In certain embodiments herein, the subject is a mammal. In other embodiments, the subject is a human.

The compositions provided herein are formulated to remain stable over a relatively long period of time. For example, the compositions provided herein are stored between -15° C. and 25° C., or between 2° C. and 8° C., and remain stable for the desired time. In one embodiment, the compositions are stored at 5° C. In other embodiment, the compositions are stored at 25° C.

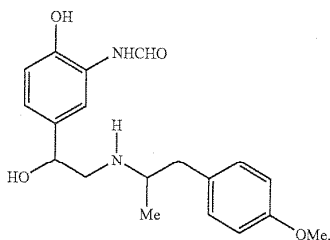
Among the bronchodilating agents for use herein are Albuterol (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); Bambuterol (dimethylcarbamic acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenylene ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetrahydro-1-(3,4,5-trimethoxyphenyl)methyl)-6,7-isoquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); Fenoterol (5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxy-5-(((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide); (R,R)-Formoterol; (S,S)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methylethyl)amino)methyl)benzenemethanol); Hexoprenaline (4,4'-(1,6-hexanediy)l-bis(imino

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(1-hydroxy-2,1-ethanediyl))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-pyridinyl)ethoxy)hexyl)-amino)methyl)benzenemethanol); Pirbuterol (α^6 -(((1,1-dimethylethyl)amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol (((R*,S*)-(\pm))-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinoline); Reproterol ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-((1R)-1-hydroxy-2-(N-((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)carbostyryl hydrochloride).

Of particular interest herein is formoterol, having the formula:



Formoterol for use in the compositions and methods provided herein includes 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof; and also includes the single enantiomers 2-hydroxy-5-(((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide.

In certain embodiments, the compositions are administered via nebulization. Administration of a nebulized aerosol is preferred over the use of dry powders for inhalation in certain subject populations, including pediatric and geriatric groups.

In one embodiment, the compositions for use in the methods provided herein contain a pharmaceutically acceptable derivative of formoterol. In another embodiment, the compositions for use in the methods provided herein contain a pharmaceutically acceptable salt of formoterol. Pharmaceutically acceptable salts include, but are not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. In one embodiment, the compositions for use in the methods provided herein contain formoterol fumarate or formoterol

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fumarate dihydrate. In another embodiment, the compositions for use in the methods provided herein contain formoterol tartrate.

Also provided herein are combinations containing a composition provided herein and a nebulizer. The combinations can be packaged as kits, which optionally contain other components, including instructions for use of the nebulizer. Any nebulizer is contemplated for use in the kits and methods provided herein. In particular, the nebulizers for use herein nebulize liquid formulations, including the compositions provided herein, containing no propellant. The nebulizer may produce the nebulized mist by any method known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or vibration. The nebulizer may further have an internal baffle. The internal baffle, together with the housing of the nebulizer, selectively removes large droplets from the mist by impaction and allows the droplets to return to the reservoir. The fine aerosol droplets thus produced are entrained into the lung by the inhaling air/oxygen.

Methods for the treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, including, but not limited to, asthma, including, but not limited to, bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness; chronic bronchitis; and other chronic obstructive pulmonary diseases are provided. The methods involve administering an effective amount of a pharmaceutical composition provided herein to a subject in need of such treatment.

Articles of manufacture, containing packaging material, a composition provided herein, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, are also provided.

DETAILED DESCRIPTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, formoterol refers to 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof. The term formoterol also refers to the single enantiomers 2-hydroxy-5-(((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide ((S,S)-formoterol) and 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide ((R,R)-formoterol).

As used herein, formoterol fumarate refers to a salt of formoterol having the formula (formoterol)- $\frac{1}{2}$ fumarate.

As used herein, formoterol free base refers to the neutral, anhydrous form of formoterol. Thus, a recitation that a composition contains, e.g., 20 μ g/mL of formoterol free base means that the composition contains 20 μ g/mL of neutral, anhydrous formoterol. Such compositions may be prepared using a derivative of formoterol.

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As used herein, an aerosol is liquid or particulate matter dispersed in air. Aerosols include dispersions of liquids, including aqueous and other solutions, and solids, including powders, in air.

As used herein, a nebulized solution refers to a solution that is dispersed in air to form an aerosol. Thus, a nebulized solution is a particular form of an aerosol.

As used herein, a nebulizer is an instrument that is capable of generating very fine liquid droplets for inhalation into the lung. Within this instrument, the nebulizing liquid or solution is atomized into a mist of droplets with a broad size distribution by methods known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or a vibrating orifice. Nebulizers may further contain, e.g., a baffle which, along with the housing of the instrument, selectively removes large droplets from the mist by impaction. Thus, the mist inhaled into the lung contains fine aerosol droplets.

As used herein, a pharmacologically suitable fluid is a solvent suitable for pharmaceutical use which is not a liquified propellant gas. Exemplary pharmacologically suitable fluids include polar fluids, including protic fluids such as water.

As used herein, a kit refers to one or more items, including, but not limited to, compounds, compositions, combinations, instruments and devices, suitably packaged for use. Kits provided herein optionally contain instructions for use.

As used herein, a combination refers to any association between two or among more items.

As used herein, fluid refers to any composition that can flow. Fluids thus encompass compositions that are in the form of semi-solids, pastes, solutions, aqueous mixtures, gels, lotions, creams and other such compositions.

As used herein, a mixture is a mutual incorporation of two or more substances, without chemical union, the physical characteristics of each of the components being retained.

As used herein, the stability of a composition provided herein refers to the length of time at a given temperature that is greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient, e.g., formoterol, is present in the composition. Thus, for example, a composition that is stable for 30 days at 25° C. would have greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient present in the composition at 30 days following storage at 25° C.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chlorprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited

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to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula $C=C(OR)$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula $C=C(OC(O)R)$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecule, in certain embodiments 1 to about 100, in other embodiments 1 to about 10, in further embodiments one to about 2, 3 or 4, solvent or water molecules. Formoterol salts and hydrates are used in certain embodiments herein.

As used herein, treatment means any manner in which one or more of the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating cancer.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, a prodrug is a compound that, upon in vivo administration, is metabolized or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, e.g., Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

It is to be understood that the compounds for use in the compositions and methods provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds for use in the compositions provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization in vivo. Thus, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization in vivo, to administration of the compound in its (S) form.

As used herein, bronchoconstriction refers to a reduction in the caliber of a bronchus or bronchi.

As used herein, undesired and/or uncontrolled bronchoconstriction refers to bronchoconstriction that results in or from a pathological symptom or condition. Pathological

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conditions include, but are not limited to, asthma and chronic obstructive pulmonary disease (COPD). Pathological symptoms include, but are not limited to, asthma and COPD.

As used herein, the statement that a composition is stable during "long term" means that the composition is suitable for administration to a subject in need thereof when it has an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C. and greater than or equal to 1, 2 or 3 years storage time at 5° C. In certain embodiments herein, using Arrhenius kinetics, >80% or >85% or >90% or >95% estimated bronchodilating agent remains after such storage. Indeed, in one preferred embodiment, the formulations of the present invention have an estimated shelf-life of greater than about 94% after 3 months storage at 25° C. and greater than about 96% after 3 months storage at 5° C.

A. Formoterol

Formoterol (2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide) is derived from adrenaline and, as noted above, is used as a β_2 -stimulator in inhalation therapy of respiratory diseases, particularly for the treatment of bronchial asthma. It has been reported that in patients with reversible obstructive respiratory diseases, formoterol has a bronchodilatory effect. This effect has a relatively rapid onset (approximately 1-3 minutes) and a relatively long duration (greater than 12 hours). Formoterol inhibits the release of leukotrienes and other messenger substances involved with inflammation, such as histamines. In addition, formoterol may bring about a hyperglycaemic activity.

To date, formoterol has been formulated as a dry powder and administered via devices such as the TURBUHALER® and the AEROLIZER®. See, e.g., Seberova et al. (2000) *Respir. Med.* 94(6):607-611; Lotvall et al. (1999) *Can. Respir. J.* 6(5):412-416; Campbell et al. (1999) *Respir. Med.* 93(4):236-244; Nightingale et al. (1999) *Am. J. Respir. Crit. Care Med.* 159(6):1786-1790; Lecaillon et al. (1999) *Eur. J. Clin. Pharmacol.* 55(2):131-138; Bartow et al. (1998) *Drugs* 55(2):303-322; Ekstrom et al. (1998) *Respir. Med.* 92(8):1040-1045; Ringdal et al. (1998) *Respir. Med.* 92(8):1017-1021; Totterman et al. (1998) *Eur. Respir. J.* 12(3):573-579; Palmqvist et al. (1997) *Eur. Respir. J.* 10(11):2484-2489; Nielsen et al. (1997) *Eur. Respir. J.* 10(9):2105-2109; Ullman et al. (1996) *Allergy* 51(10):745-748; Selroos et al. (1996) *Clin. Immunother.* 6:273-299; and Schreurs et al. (1996) *Eur. Respir. J.* 9(8):1678-1683.

Formoterol is also available as a tablet and a dry syrup in certain areas of the world (e.g., ATOCK®, marketed by Yamanouchi Pharmaceutical Co. Ltd., Japan). Formoterol formulations are also available in other areas (e.g., Europe and U.S.) for propellant-based metered dose inhalers and dry powder inhalers (e.g., TURBUHALER®, AEROLIZER® AND FORADIL AEROLIZER®). None of these formulations are water based. Sterile, stable, aqueous based inhalation solutions of formoterol for nebulization are not available, nor have they been reported.

In the treatment of bronchoconstrictive diseases, sufficient amount of the inhaled drug should reach their local site of action in order to be efficacious. It is known that different delivery methods and delivery devices have different deposition characteristics. Consequently, under optimal inhalation conditions, doses from different delivery methods and delivery devices result in different delivered doses and different amounts deposited at the active site. The actual dose reaching the active site also depends upon the amount of drug particles included in the delivered dose and the inhalation

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characteristics of the patient. No correlation between the amount of drug administered by dry powder inhalers (DPIs) or metered dose inhalers (MDIs) and the actual amount that gets deposited at the active site has been established so far. Nor has a correlation been established between DPI or MDI dosages and nebulization dosages.

Compositions containing formoterol in combination with other active ingredients have been disclosed. See, e.g., U.S. Pat. Nos. 6,004,537, 5,972,919 and 5,674,860 (formoterol and budesonide), U.S. Pat. Nos. 5,668,110, 5,683,983, 5,677,280 and 5,654,276 (formoterol and IL-5 inhibitors), U.S. Pat. No. 6,136,603 (formoterol and antisense modulators of IL-5), U.S. Pat. No. 5,602,110 (formoterol and millrinone), U.S. Pat. No. 5,525,623 (formoterol and a tryptase inhibitor), U.S. Pat. Nos. 5,691,336, 5,877,191, 5,929,094, 5,750,549 and 5,780,467 (formoterol and a tachykinin receptor antagonist); and International Patent Application Publication Nos. WO 99/00134 (formoterol and rofleponide) and WO 99/36095 (formoterol and a dopamine D_2 receptor agonist).

Other compositions containing formoterol have been disclosed in U.S. Pat. Nos. 5,677,809, 6,126,919, 5,733,526, 6,071,971, 6,068,833, 5,795,564, 6,040,344, 6,041,777, 5,874,481, 5,965,622 and 6,161,536.

U.S. Pat. No. 6,150,418 discloses a "liquid active substance concentrate" containing formoterol in the form of its free base or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as active substance. This "liquid active substance concentrate" is reported to be a concentrated (i.e., greater than 10 mg/mL, preferably 75 to 500 mg/mL) solution or suspension that is stable for a period of several months possibly up to several years without any deterioration in the pharmaceutical quality. This patent teaches that it is the high concentration that allows for the stability of the concentrate. The "liquid active substance concentrate" is not suitable for direct administration to a patient.

U.S. Pat. No. 6,040,344 discloses an aqueous aerosol formulation of formoterol tartrate for use in a nebulizer. This patent states that the formulation disclosed therein is not attractive for long term storage.

B. Compositions for Use in Treatment, Prevention, or Amelioration of One or More Symptoms of Bronchoconstrictive Disorders

Pharmaceutical compositions containing a β_2 -adrenoreceptor agonist for administration via nebulization are provided. The compositions are sterile filtered and filled in vials, including unit dose vials providing sterile unit dose formulations which are used in a nebulizer and suitably nebulized. Each unit dose vial is sterile and is suitably nebulized without contaminating other vials or the next dose.

The unit dose vials are formed in a form-fill-seal machine or by any other suitable method known to those of skill in the art. The vials may be made of plastic materials that are suitably used in these processes. For example, plastic materials for preparing the unit dose vials include, but are not limited to, low density polyethylene, high density polyethylene, polypropylene and polyesters. In one embodiment, the plastic material is low density polyethylene.

In one embodiment, the β_2 -adrenoreceptor agonist is formoterol, or a pharmaceutically acceptable derivative thereof. In other embodiments, the formoterol for use in the compositions provided herein is formoterol fumarate. Formoterol refers to 2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanil-

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ide; or a stereoisomer thereof. The term formoterol also refers herein to the single enantiomers 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide.

In certain embodiments, the compositions contain formoterol fumarate at a concentration of about 0.1 $\mu\text{g/mL}$ up to about 150 $\mu\text{g/mL}$, or 0.1 $\mu\text{g/mL}$ up to 150 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol fumarate at a concentration of about 0.1 $\mu\text{g/mL}$ up to about 100 $\mu\text{g/mL}$, or 0.1 $\mu\text{g/mL}$ up to 100 $\mu\text{g/mL}$. The formoterol fumarate is formulated, in certain compositions provided herein, at a concentration of about 0.1 $\mu\text{g/mL}$ up to 50 $\mu\text{g/mL}$, or 0.1 $\mu\text{g/mL}$ up to 50 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol fumarate at a concentration of about 0.1 $\mu\text{g/mL}$ up to about 40 $\mu\text{g/mL}$, or 0.1 $\mu\text{g/mL}$ up to 40 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol fumarate at a concentration of about 0.1 $\mu\text{g/mL}$ up to about 20 $\mu\text{g/mL}$, or 0.1 $\mu\text{g/mL}$ up to 20 $\mu\text{g/mL}$. The formoterol fumarate is formulated, in other compositions provided herein, at a concentration of about 40 $\mu\text{g/mL}$, or 40 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol fumarate at a concentration of about 35 $\mu\text{g/mL}$, or 35 $\mu\text{g/mL}$. In other embodiments, the compositions contain formoterol fumarate at a concentration of about 30 $\mu\text{g/mL}$, or 30 $\mu\text{g/mL}$. In other embodiments, the compositions contain formoterol fumarate at a concentration of about 25 $\mu\text{g/mL}$, or 25 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol fumarate at a concentration of about 20 $\mu\text{g/mL}$, or 20 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol fumarate at a concentration of about 15 $\mu\text{g/mL}$, or 15 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol fumarate at a concentration of about 12 $\mu\text{g/mL}$, or 12 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol fumarate at a concentration of about 10 $\mu\text{g/mL}$, or 10 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol fumarate at a concentration of about 8 $\mu\text{g/mL}$, or 8 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol fumarate at a concentration of about 5 $\mu\text{g/mL}$, or 5 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol fumarate at a concentration of about 2.5 $\mu\text{g/mL}$, or 2.5 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol fumarate at a concentration of about 1 $\mu\text{g/mL}$, or 1 $\mu\text{g/mL}$.

In certain embodiments, the compositions contain formoterol free base at a concentration of about 0.08 $\mu\text{g/mL}$ up to about 128 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 128 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol free base at a concentration of about 0.08 $\mu\text{g/mL}$ up to about 86 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 86 $\mu\text{g/mL}$. The formoterol free base is formulated, in certain compositions provided herein, at a concentration of about 0.08 $\mu\text{g/mL}$ up to 43 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 43 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol free base at a concentration of about 0.08 $\mu\text{g/mL}$ up to about 34 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 34 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol free base at a concentration of about 0.08 $\mu\text{g/mL}$ up to about 26 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 26 $\mu\text{g/mL}$. The formoterol free base is formulated, in other compositions provided herein, at a concentration of about 0.08 $\mu\text{g/mL}$ up to about 17 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 17 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol free base at a concentration of about 34 $\mu\text{g/mL}$, or 34 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol free base at a concentration of about 30 $\mu\text{g/mL}$,

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or 30 $\mu\text{g/mL}$. In other embodiments, the compositions contain formoterol free base at a concentration of about 25.6 $\mu\text{g/mL}$, or 25.6 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol free base at a concentration of about 21.4 $\mu\text{g/mL}$, or 21.4 $\mu\text{g/mL}$. In further embodiments, the compositions contain formoterol free base at a concentration of about 17 $\mu\text{g/mL}$, or 17 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol free base at a concentration of about 13 $\mu\text{g/mL}$, or 13 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol free base at a concentration of about 10 $\mu\text{g/mL}$, or 10 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol free base at a concentration of about 9 $\mu\text{g/mL}$, or 9 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol free base at a concentration of about 7 $\mu\text{g/mL}$, or 7 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol free base at a concentration of about 4 $\mu\text{g/mL}$, or 4 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol free base at a concentration of about 2 $\mu\text{g/mL}$, or 2 $\mu\text{g/mL}$. In another embodiment, the compositions contain formoterol free base at a concentration of about 0.8 $\mu\text{g/mL}$, or 0.8 $\mu\text{g/mL}$.

The volume of formoterol inhalation solution nebulized depends on the nebulizer used. In certain embodiments, the volume is from about 0.1 mL up to about 3 mL, or 0.1 mL up to 3 mL. In other embodiments, the volume is about 2 mL, or 2 mL. In other embodiments, the volume is about 1 mL, or 1 mL. In other embodiments, the volume is about 0.5 mL, or 0.5 mL.

The compositions containing the β_2 -adrenoreceptor agonist, including formoterol, are formulated with a pharmacologically suitable fluid. Pharmacologically suitable fluids include, but are not limited to, polar solvents, including, but not limited to, compounds that contain hydroxyl groups or other polar groups. Such solvents include, but are not limited to, water or alcohols, such as ethanol, isopropanol, and glycols including propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol and polyoxyethylene alcohols.

Polar solvents also include protic solvents, including, but not limited to, water, aqueous saline solutions with one or more pharmaceutically acceptable salt(s), alcohols, glycols or a mixture thereof. For a saline solution as the solvent or as a component thereof, particularly suitable salts are those which display no or only negligible pharmacological activity after administration.

In the embodiments herein, the compositions have a pH of about 2.0 to about 8.0, or 2.0 to 8.0. In other embodiments, the compositions have a pH of about 4.0 to about 6.0, or 4.0 to 6.0. In other embodiments, the pH is about 4.5 to about 5.5, or 4.5 to 5.5. In certain of the above embodiments, the compositions are formulated at a pH of about 4, 4.4 or 4.6 up to about 5.5, 5.7 or 6; or 4, 4.4 or 4.6 up to 5.5, 5.7 or 6. In other embodiments, the pH is about 5.0, or 5.0. It has been found that the rate constant for decomposition of an aqueous solution of formoterol is dependent on pH. The rate constant (k_{obs}) at 60° C. at a pH of 3, 4, 5 and 7 is approximately 0.62, 0.11, 0.044 and 0.55 day^{-1} , respectively. Therefore, the decomposition of formoterol in aqueous solution at 60° C. at a buffer concentration of 5 mM and an ionic strength of 0.05 is slowest at a pH of about 5.0, or 5.0.

The solubility of formoterol in aqueous solution has been found to be dependent on pH. Thus, at a pH of between about 5 and about 7, the aqueous solubility of formoterol at ambient temperature is approximately 2.2 mg/mL. At a pH of about 4, the aqueous solubility of formoterol at ambient temperature is approximately 3 mg/mL, while at a pH of

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about 3, the aqueous solubility of formoterol at ambient temperature is about 4.8 mg/mL. The solubility of formoterol in pure water, for example, high performance liquid chromatography (HPLC) water, at ambient temperature is approximately 2 mg/mL.

In other of the above embodiments, the compositions further contain a buffer, including, but not limited to, citric acid/phosphate, acetate, barbitol, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Pridaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris-(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BISTRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)), DIPS (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)-butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), TRIZMA® (tris(hydroxymethylaminomethane)), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid)), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid)), TRICINE (N-tris(hydroxy-methyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanedisulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), AMPD (2-amino-2-methyl-1,3-propanediol), and/or any other buffers known to those of skill in the art. In one embodiment, the buffer is citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer. In another embodiment, the buffer is a citrate buffer (citric acid/sodium citrate). The buffer concentration has been found to affect the stability of the composition. Buffer concentrations for use include from about 0 or 0.01 mM to about 150 mM, or 0 or 0.01 mM to 150 mM. In another embodiment, the buffer concentration is about 1 mM to about 20 mM, or 1 mM to 20 mM. In one embodiment, the buffer concentration is about 5 mM, or 5 mM. In other embodiments, the buffer concentration is about 1 mM to about 50 mM, or 1 mM to 50 mM. In one embodiment, the buffer concentration is about 20 mM, or 20 mM. The kinetic-pH profile of formoterol is dependent on buffer concentration. At low and approximately neutral conditions, increasing the buffer concentration from 5 mM to 20 mM increased the rate constant of decomposition significantly. However, no noticeable differences in rate constant were observed in the pH region of about 4.5 to about 5.5, with increasing buffer concentration from 5 mM to 20 mM. The particular buffer and buffer concentration of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, e.g., the Examples).

The ionic strength of the compositions provided herein also has been found to affect the stability of the composition. Ionic strengths of the compositions provided herein are from about 0 to about 0.4, or 0 to 0.4. In another embodiment, the ionic strength of the compositions provided is about 0.05 to about 0.16, or 0.05 to 0.16. Compositions having a lower

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ionic strength exhibit improved stability over formulations having higher ionic strength. The rate constant of decomposition was essentially the same at ionic strength 0.05 to 0.1, but increased to some extent at ionic strength of 0.2. The particular ionic strength of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, e.g., the Examples).

In embodiments where the pharmacologically suitable fluid is a saline solution, tonicity adjusting agents may be added to provide the desired ionic strength. Tonicity adjusting agents for use herein include those which display no or only negligible pharmacological activity after administration. Both inorganic and organic tonicity adjusting agents may be used in the compositions provided herein. Tonicity adjusting agents include, but are not limited to, ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethane, uridine and zinc sulfate. In certain embodiments, the tonicity adjusting agent is sodium chloride. In these embodiments, the pharmacologically suitable fluid is aqueous saline.

The storage temperature of the compositions provided herein also has been found to affect the stability of the composition. Compositions stored at a lower temperature exhibit improved stability over formulations stored at higher temperatures. The effect of temperature on the rate constant of decomposition at pH 5, a buffer concentration of 5 mM, and an ionic strength of 0.05, was linear according to Arrhenius kinetics, i.e., when $\ln k_{obs}$ was plotted against $1/T$, where T is the temperature in degree Kelvin.

The estimated shelf-life of formoterol in the compositions provided herein is significantly greater than that reported for known formoterol compositions. The estimated shelf-life of formoterol in the compositions provided herein is about 6.2 years, at 5° C. and about 7.5 months, or at 25° C. The estimated formoterol concentrations in the compositions provided herein as a function of storage time at 5° C. and usage time at 25° C. was determined. It is estimated that greater than 90% of the initial formoterol present in the composition remains after 3 months of usage time at 25° C. and 3 years of storage time at 5° C. as well as after 0.5 months of usage time at 25° C. and 1 year of storage time at 5° C.

In one embodiment, the compositions provided herein are prepared containing formoterol fumarate at a nominal concentration of 0.1 mg/mL at the indicated pH and citric acid/phosphate buffer concentrations. The solutions were stored at 60° C. In these compositions, formoterol is rela-

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tively more stable at a pH from about 4 to about 5, and is also more stable at lower buffer concentration.

The compositions provided herein also may include excipients and additives. The particular excipient or additive for use in the compositions for long term storage provided herein may be determined empirically using methods well known to those of skill in the art (see, e.g., the Examples). Excipients and additives are any pharmacologically suitable and therapeutically useful substance which is not an active substance. Excipients and additives generally have no pharmacological activity, or at least no undesirable pharmacological activity. The excipients and additives include, but are not limited to, surfactants, stabilizers, complexing agents, antioxidants, or preservatives which prolong the duration of use of the finished pharmaceutical formulation, flavorings, vitamins, or other additives known in the art. Complexing agents include, but are not limited to, ethylenediaminetetraacetic acid (EDTA) or a salt thereof, such as the disodium salt, citric acid, nitrilotriacetic acid and the salts thereof. In one embodiment, the complexing agent is EDTA. Preservatives include, but are not limited to, those that protect the solution from contamination with pathogenic particles, including benzalkonium chloride or benzoic acid, or benzoates such as sodium benzoate. Antioxidants include, but are not limited to, vitamins, provitamins, ascorbic acid, vitamin E or salts or esters thereof.

The compositions provided herein also may include a cosolvent, which increases the solubility of additives or the active ingredient(s). The particular cosolvent for use in the compositions for long term storage provided herein may be determined empirically using methods well known to those of skill in the art. Cosolvents for use herein include, but are not limited to, hydroxylated solvents or other polar solvents, such as alcohols such as isopropyl alcohol, glycols such as propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol, and polyoxyethylene alcohols.

C. Preparation of Compounds for Use in the Compositions

The preparation of the compounds used in the compositions provided herein is described below. Any such compound or similar compound may be synthesized according to a method discussed in general below or by only minor modification of the methods by selecting appropriate starting materials.

Formoterol may be prepared according to the method disclosed in U.S. Pat. No. 3,994,974. Briefly, 4-benzyloxy-3-nitro- α -bromoacetophenone is reacted with N-benzyl-N-(1-methyl-2-p-methoxyphenylethyl)amine to form the α -aminoacetophenone. This compound was subjected to the following series of reactions: (i) reduction of the ketone with sodium borohydride; (ii) reduction of the nitro group with aqueous hydrochloric acid and iron powder; (iii) amine formylation with acetic anhydride and formic acid; and (iv) catalytic reduction over 10% palladium on carbon to afford formoterol free base. Crystallization of the $\frac{1}{2}$ fumarate salt from ethanol provides (formoterol)- $\frac{1}{2}$ fumarate.

The individual enantiomers of formoterol, 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide, may be prepared by the method disclosed in U.S. Pat. No. 6,040,344. Briefly, reaction of optically pure 4-benzyloxy-3-formamidostyrene oxide with an optically pure 4-methoxy- α -methyl-N-(phenylmethyl)benzeneethanamine, followed by debenzilation, affords the desired enantiomer of formoterol. Debenzilation may be accom-

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plished by reduction with hydrogen gas in the presence of a noble metal catalyst, such as palladium on carbon.

The required optically pure 4-benzyloxy-3-formamidostyrene oxide may be prepared from 4-benzyloxy-3-nitro- α -bromoacetophenone by (i) reduction with vorane in the presence of an optically pure aminoindanol, (ii) hydrogenation over platinum oxide catalyst, (iii) formylation with formic acid and acetic anhydride, and (iv) epoxide formation in the presence of potassium carbonate.

The required optically pure 4-methoxy- α -methyl-N-(phenylmethyl)benzeneethan-amine may be prepared from 4-methoxyphenylacetone by (i) reductive amination with benzylamine in the presence of hydrogen and a platinum catalyst, and (ii) crystallization of the desired optically pure amine from the resulting racemic mixture as its mandelic acid salt.

D. Formulation of Pharmaceutical Compositions

The compositions provided herein are prepared by procedures well known to those of skill in the art. For example, a formoterol fumarate solution may be prepared by the procedure of EXAMPLE 1. Briefly, a buffer solution having a pH and ionic strength of interest herein is prepared. In one embodiment, the buffer is a mixture of citric acid and sodium citrate, with sodium chloride added to achieve the desired ionic strength. Formoterol fumarate dihydrate is added to the buffer solution with agitation to produce a solution of the desired formoterol concentration. Exemplary formoterol concentrations are 0.0021 kg formoterol fumarate dihydrate/100 kg water.

E. Evaluation of the Activity of the Compositions

Standard physiological, pharmacological and biochemical procedures are available for testing the compositions provided herein to identify those that possess bronchodilatory activity.

In vitro and in vivo assays that may be used to evaluate bronchodilatory activity are well known to those of skill in the art. See also, e.g., U.S. Pat. Nos. 3,994,974, and 6,068,833; German Patent No. 2,305,092; Kaumann et al. (1985) *Naunyn-Schmied Arch. Pharmacol.* 331:27-39; Lemoine et al. (1985) *Naunyn-Schmied Arch. Pharmacol.* 331:40-51; Tomioka et al. (1981) *Arch. Int. Pharmacodyn.* 250:279-292; Dellamary et al. (2000) *Pharm. Res.* 17(2):168-174; Rico-Mendez et al. (1999) *Rev. Alerg. Mex.* 46(5):130-135; Seberova et al. (2000) *Respir. Med.* 94(6):607-611; Lotvall et al. (1999) *Can. Respir. J.* 6(5):412-416; Campbell et al. (1999) *Respir. Med.* 93(4):236-244; Nightingale et al. (1999) *Am. J. Respir. Crit. Care Med.* 159(6):1786-1790; Lecaillon et al. (1999) *Eur. J. Clin. Pharmacol.* 55(2):131-138; Bartow et al. (1998) *Drugs* 55(2):303-322; Ekstrom et al. (1998) *Respir. Med.* 92(8):1040-1045; Ringdal et al. (1998) *Respir. Med.* 92(8):1017-1021; Totterman et al. (1998) *Eur. Respir. J.* 12(3):573-579; Palmqvist et al. (1997) *Eur. Respir. J.* 10(11):2484-2489; Nielsen et al. (1997) *Eur. Respir. J.* 10(9):2105-2109; Ullman et al. (1996) *Allergy* 51(10):745-748; Selroos et al. (1996) *Clin. Immunother.* 6:273-299; and Schreurs et al. (1996) *Eur. Respir. J.* 9(8):1678-1683.

F. Methods of Treatment of Bronchoconstrictive Disorders

The compositions provided herein are used for treating, preventing, or ameliorating one or more symptoms of a bronchoconstrictive disorders in a subject. In one embodiment, the method includes administering to a subject an effective amount of a composition containing a bronchodilating agent, including, but not limited to, formoterol, whereby the disease or disorder is treated or prevented. The

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subject treated is, in certain embodiments, a mammal. The mammal treated is, in certain embodiments, a human.

In another embodiment, the method provided herein includes oral administration of a composition provided herein. In certain embodiments herein, the composition is directly administered to a subject in need of such treatment via nebulization without dilution or other modification of the composition prior to administration.

The methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, in another embodiment, further include administering one or more of (a), (b), (c) or (d) as follows: (a) a β_2 -adrenoreceptor agonist; (b) a dopamine (D_2) receptor agonist; (c) a prophylactic therapeutic, such as a steroid; or (d) an anticholinergic agent; simultaneously with, prior to or subsequent to the composition provided herein.

β_2 -Adrenoreceptor agonists for use in combination with the compositions provided herein include, but are not limited to, Albuterol (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); Bambuterol (dimethylcarbamic acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenylene ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetrahydro-1-((3,4,5-trimethoxyphenyl)methyl)-6,7-isquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); Fenoterol (5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxy-5-((1R)-1-hydroxy-2-((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)-formanilide); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methylethyl)amino)methyl)benzenemethanol); Hexoprenaline (4,4'-((1,6-hexanediy)bis(imino(1-hydroxy-2,1-ethanediy)))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(pyridinyl)ethoxy)hexyl)amino)methyl)benzenemethanol); Pirbuterol (α^1 -(((1,1-dimethylethyl)amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol (((R*,S*)-(\pm)-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolinone); Reproterol ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)-propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)-methyl)-4-hydroxy-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-((1R)-1-hydroxy-2-(N-((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)carbostyryl hydrochloride).

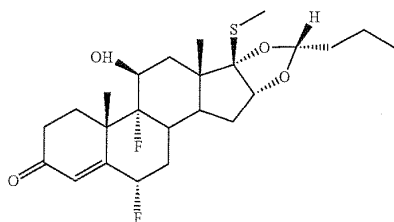
Dopamine (D_2) receptor agonists include, but are not limited to, Apomorphine ((r)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo[de,g]quinoline-10,11-diol); Bromocriptine ((5 α)-2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)ergotaman-3',6',18-trione); Cabergoline ((8 β)-N-(3-(dimethylamino)propyl)-N-((ethylamino)carbonyl)-6-(2-propenyl)ergoline-8-carboxamide); Lisuride (N'-(8 α)-9,10-

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didehydro-6-methylergolin-8-yl)-N,N-diethylurea); Pergolide ((8 β)-8-((methylthio)methyl)-6-propylergoline); Levodopa (3-hydroxy-L-tryrosine); Pramipexole ((s)-4,5,6,7-tetrahydro-N⁶-propyl-2,6-benzothiazolediamine); Quinpirole hydrochloride (trans-(-)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo[3,4-g]quinoline hydrochloride); Ropinirole (4-(2-(dipropylamino)ethyl)-1,3-dihydro-2H-indol-2-one); and Talipexole (5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thiazolo[4,5-d]azepin-2-amine).

Other dopamine D_2 receptor agonists for use herein are disclosed in International Patent Application Publication No. WO 99/36095.

Prophylactic therapeutics for use in combination therapy herein include steroidal anti-inflammatory agents, including, but not limited to, beclomethasone dipropionate (BDP), beclomethasone monopropionate (BMP), flunisolide, triamcinolone acetonide, dexamethasone, tripredane, ciclesonid, rofleponide, mometasone, mometasone furoate (AS-MANEX® TWISTHALER™, Schering-Plough Corporation, Kenilworth, N.J.), RPR 106541, having the formula



fluticasone or fluticasone propionate and budesonide or by way of sodium cromoglycate or nedocromil sodium.

Anticholinergic agents for use herein include, but are not limited to, ipratropium bromide, oxitropium bromide, atropine methyl nitrate, atropine sulfate, ipratropium, belladonna extract, scopolamine, scopolamine methobromide, homatropine methobromide, hyoscyamine, isopropamide, orphenadrine, benzalkonium chloride, tiotropium bromide and glycopyrronium bromide. In certain embodiments, the compositions contain an anticholinergic agent, such as ipratropium bromide, at a concentration of about 100 μ g/mL to about 500 μ g/mL, or 100 μ g/mL to 500 μ g/mL. In other embodiments, ipratropium bromide concentration is about 150 μ g/mL to about 350 μ g/mL, or 150 μ g/mL to 350 μ g/mL. In other embodiments, the compositions for use in the methods herein contain ipratropium bromide at a concentration of about 250 μ g/mL, or 250 μ g/mL.

Other active ingredients for use herein in combination therapy, include, but are not limited to, IL-5 inhibitors such as those disclosed in U.S. Pat. Nos. 5,668,110, 5,683,983, 5,677,280 and 5,654,276; antisense modulators of IL-5 such as those disclosed in U.S. Pat. No. 6,136,603; milrinone (1,6-dihydro-2-methyl-6-oxo-3,4'-bipyridine)-5-carbonitrile milrinone lactate; trypsin inhibitors such as those disclosed in U.S. Pat. No. 5,525,623; tachykinin receptor antagonists such as those disclosed in U.S. Pat. Nos. 5,691,336, 5,877,191, 5,929,094, 5,750,549 and 5,780,467; leukotriene receptor antagonists such as montelukast sodium (SINGULAR®, R-(E))-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)]

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ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]-propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt), 5-lipoxygenase inhibitors such as zileuton (ZYFLO®, Abbott Laboratories, Abbott Park, Ill.), and anti-IgE antibodies such as XOLAIR® (recombinant humanized anti-IgE monoclonal antibody (CGP 51901; IGE 025A; rhuMAb-E25), Genentech, Inc., South San Francisco, Calif.).

The bronchoconstrictive disorder to be treated, prevented, or whose one or more symptoms are to be ameliorated is associated with asthma, including, but not limited to, bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness; and, particularly in embodiments where an anticholinergic agent is used, other chronic obstructive pulmonary diseases (COPDs), including, but not limited to, chronic bronchitis, emphysema, and associated cor pulmonale (heart disease secondary to disease of the lungs and respiratory system) with pulmonary hypertension, right ventricular hypertrophy and right heart failure. COPD is frequently associated with cigarette smoking, infections, environmental pollution and occupational dust exposure.

G. Nebulizers

The compositions provided herein are intended for administration to a subject in need of such treatment via nebulization. Nebulizers that nebulize liquid formulations containing no propellant are suitable for use with the compositions provided herein. The nebulizer and can be unit dose or multidose. Nebulizers are available from, e.g., Pari GmbH (Starnberg, Germany), DeVilbiss Healthcare (Heston, Middlesex, UK), Healthdyne, Vital Signs, Baxter, Allied Health Care, Invacare, Hudson, Omron, Bmed, AirSep, Luminscope, Medisana, Siemens, Aerogen, Mountain Medical, Aerosol Medical Ltd. (Colchester, Essex, UK), AFP Medical (Rugby, Warwickshire, UK), Bard Ltd. (Sunderland, UK), Carri-Med Ltd. (Dorking, UK), Plaem Nuiva (Brescia, Italy), Henleys Medical Supplies (London, UK), Intersurgical (Berkshire, UK), Lifecare Hospital Supplies (Leies, UK), Medic-Aid Ltd. (West Sussex, UK), Medix Ltd. (Essex, UK), Sinclair Medical Ltd. (Surrey, UK), and many others.

Nebulizers for use herein include, but are not limited to, jet nebulizers (optionally sold with compressors), ultrasonic nebulizers, and others. Exemplary jet nebulizers for use herein include Pari LC plus/ProNeb, Pari LC plus/ProNeb Turbo, Pari LC plus/Dura Neb 1000 & 2000, Pari LC plus/Walkhaler, Pari LC plus/Pari Master, Pari LC star, Omron CompAir XL Portable Nebulizer System (NE-C 18 and JetAir Disposable nebulizer), Omron CompAir Elite Compressor Nebulizer System (NE-C21 and Elite Air Reusable Nebulizer), Pari LC Plus or Pari LC Star nebulizer with Proneb Ultra compressor, Pulmo-aide, Pulmo-aide LT, Pulmo-aide traveler, Invacare Passport, Inspiration Healthdyne 626, Pulmo-Neb Traverler, DeVilbiss 646, Whisper Jet, Acorn II, Misty-Neb, Allied aerosol, Schuco Home Care, Lexan Plastic Pocet Neb, SideStream Hand Held Neb, Mobil Mist, Up-Draft, Up-Draft II, T Up-Draft, ISO-NEB, AVA-NEB, Micro Mist, and PulmoMate. Exemplary ultrasonic nebulizers for use herein include MicroAir, UltraAir, Siemens Ultra Nebulizer 145, CompAir, Pulmosonic, Scout, 5003 Ultrasonic Neb, 5110 Ultrasonic Neb, 5004 Desk Ultrasonic Nebulizer, Mystique Ultrasonic, Luminscope's Ultrasonic Nebulizer, Medisana Ultrasonic Nebulizer, Microstat Ultrasonic Nebulizer, and MABISMist Hand Held Ultrasonic Nebulizer. Other nebulizers for use herein include 5000 Electromagnetic Neb, 5001 Electromagnetic

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Neb 5002 Rotary Piston Neb, Lumineb I Piston Nebulizer 5500, AERONEB™ Portable Nebulizer System, AERODOSE™ Inhaler, AeroEclipse Breath Actuated Nebulizer, HALOLITE™ system (Profile Therapeutics), AKITA® systems (InaMed, Germany), Mystic system (BattellePharma), RESPIMAT® (Boehringer Ingelheim), AERX® (Aradigm), and E-FLOW™ (Pari).

Depending on the nebulizer used, the volume of the formoterol inhalation solution nebulized in one embodiment, is about 0.1 mL to 3 mL, or 0.1 mL to 3 mL. In another embodiment, the volume is about 2 mL, or 2 mL. In another embodiment, the volume is about 1 mL, or 1 mL. In another embodiment, the volume is about 0.5 mL, or 0.5 mL.

H. Articles of Manufacture

The compositions provided herein may be packaged as articles of manufacture containing packaging material, a composition provided herein, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

In one embodiment herein, the compositions are packaged with a nebulizer for direct administration of the composition to a subject in need thereof.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1

Preparation of Formoterol Inhalation Solution Formulation:

Appropriate quantities of the raw materials are weighed for the 100 Kg batch as shown below:

	20 µg/mL*	10 µg/mL*
Formoterol fumarate dihydrate	0.0021 kg	0.00105 kg
Citric acid monohydrate USP	0.135 kg	0.135 kg
Sodium Citrate dihydrate USP	0.400 kg	0.400 kg
Sodium chloride USP	0.785 kg	0.785 kg
Purified water USP	q.s. to 100 kg	q.s. to 100 kg

*Concentration of formoterol fumarate (anhydrous)

In a clean stainless steel (SS) tank fitted with bottom drain, 75% of the required amount of purified water is added. Samples are taken for pH, conductivity, and microbiological testing. Citric acid monohydrate, sodium citrate dihydrate and sodium chloride are added to the tank and mixed for 15 minutes to dissolve. A sample is taken at this point to check pH. Formoterol fumarate dihydrate is added at this point and mixed for about 75 minutes to dissolve all active raw material. Purified water is used to adjust to final volume. The formulation is mixed for an additional 30 minutes and

samples for pH and assay are taken based on which the formulation is released for filling. The bulk solution is filled into low density polyethylene (LDPE) vials (2 mL fill) in a form-fill-seal (FFS) machine. The released drug product solution is transferred from the formulation tank through sanitary delivery lines into the FFS machine. The individual vials are overwrapped with a suitable foil laminate.

EXAMPLE 2

Procedure for Stability Testing of Formoterol Solutions

Stability samples of the solution prepared in EXAMPLE 1 and solution of formoterol fumarate (20 µg/mL) and ipratropium bromide (250 µg/mL) were placed in LDPE vials and stored in stability ovens at accelerated temperatures. At selected time points, aliquots of the samples were removed from the vials. The formoterol concentrations of the samples were analyzed by high performance liquid chromatography.

Provided herein is the stability data for exemplary formulations containing formoterol and formoterol in combination with ipratropium bromide.

Stability Data on Formoterol (20 µg/mL) and Formoterol Fumarate/Ipratropium Bromide Combination (20 µg/ml and 250 µg/mL):

Storage condition	Assay as percent of label claim		
	Formoterol Inhalation solution	Formoterol fumarate/pratropium bromide inhalation solution	
		Formoterol	Ipratropium
Initial	100	100.5	101.2
5° C./3 months	96.7	100	101.6
25° C./3 months	94.5	100	101.2

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

What is claimed is:

1. A sterile unit dose, comprising:

(a) about 0.1 mL to about 3.0 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 µg/mL to about 34 µg/mL based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a buffer selected from the group consisting of citric acid/phosphate buffer, acetate buffer, citrate buffer and phosphate buffer at a concentration of from about 1 mM to about 20 mM, said composition having a pH of between about 4.5 and about 5.5 and having an estimated shelf life of greater than 90% after 3 months storage at 25° C. and after 3 years storage at 5° C.;

(b) packaged in pharmaceutical packaging material.

2. A sterile unit dose, comprising:

(a) about 0.1 mL to about 3.0 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 $\mu\text{g/mL}$ to about 34 $\mu\text{g/mL}$ based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a buffer selected from the group consisting of citric acid/phosphate buffer, acetate buffer, citrate buffer and phosphate buffer at a concen-

tration of from about 5 mM to about 20 mM, said composition having a pH of between about 4.5 and about 5.5 and having an estimated shelf life of greater than about 94% after 3 months storage at 25° C. and greater than about 96% after 3 months storage at 5° C.;

(b) packaged in pharmaceutical packaging material.

3. A sterile unit dose, comprising:

(a) about 2 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 $\mu\text{g/mL}$ to about 26 $\mu\text{g/mL}$ based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a citrate buffer at a concentration of from about 1 mM to about 20 mM, said composition having a pH of about 5, and having an estimated shelf life of greater than about 94% after 3 months storage at 25° C. and greater than about 96% after 3 months storage at 5° C.;

(b) packaged in a vial over wrapped with a laminate.

4. A sterile unit dose, comprising:

(a) about 2 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 $\mu\text{g/mL}$ to about 26 $\mu\text{g/mL}$ based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a citrate buffer at a concentration of from about 1 mM to about 50 mM, said composition having a pH of about 5;

(b) packaged in a vial over wrapped with a laminate.

5. The sterile unit dose as in any one of claims 1, 2, 3 or 4 further comprising a tonicity adjusting agent.

6. The sterile unit dose of claim 5 wherein said tonicity adjusting agent is sodium chloride.

7. The sterile unit dose as in any one of claims 1 or 2 wherein said pharmaceutical packaging material is selected from the group consisting of blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers and syringes.

8. A method of oral administration comprising the steps of:

(a) adding to a nebulizer, from a propellant-free, sterile unit dose package about 1 to about 3 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 $\mu\text{g/mL}$ to about 34 $\mu\text{g/mL}$ based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a buffer selected from the group consisting of citric acid/phosphate buffer, acetate buffer, citrate buffer and phosphate buffer at a concentration of from about 1 mM to about 50 mM, said composition having a pH of between about 4.5 and about 5.5; and

(b) directly administering said composition to a subject in need thereof, without dilution or other modification of said composition prior to administration.

9. A method of oral administration comprising the steps of:

(a) adding to a nebulizer from a propellant-free, sterile unit dose package about 1 to about 3 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 $\mu\text{g/mL}$ to about 34 $\mu\text{g/mL}$ based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a buffer selected from the group consisting of citric acid/phosphate buffer, acetate buffer, citrate buffer and phosphate buffer at a concentration of from about 1 mM to about 50 mM, said composition having a pH of between

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- about 4.5 and about 5.5 and having an estimated shelf life of greater than 90% after 3 months storage at 25° C. and after 3 years storage at 5° C.; and
- (b) directly administering said composition to a subject in need thereof, without dilution or other modification of said composition prior to administration.
10. A method of oral administration comprising the steps of:
- (a) adding from a propellant-free, sterile unit dose package to a nebulizer about 2 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 µg/mL to about 26 µg/mL based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a citrate buffer at a concentration of from about 1 mM to about 20 mM, said composition having a pH of about 5 and having an estimated shelf life of greater than about 94% after 3 months storage at 25° C. and greater than about 96% after 3 months storage at 5° C.; and
- (b) directly administering said composition to a subject in need thereof, without dilution or other modification of said composition prior to administration.

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11. The method of claims 8, 9, or 10 further comprising a tonicity adjusting agent.
12. The method of claim 11 wherein said tonicity adjusting agent is sodium chloride.
13. The method as in any one of claims 8, 9 or 10 wherein said package is selected from the group consisting of blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers and syringes.
14. The method as in any one of claims 8, 9 or 10 wherein said package is a vial.
15. The method of claim 14 wherein said vial is over wrapped with a laminate.
16. The sterile unit dose of claim 1 wherein said formoterol is in the (R) form, or a salt thereof.
17. The sterile unit dose of claim 16 wherein said (R) formoterol is a salt and said salt is a tartrate.
18. The sterile unit dose of claim 1 wherein said formoterol is a tartrate salt.

* * * * *

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TO ALL TO WHOM THESE PRESENTS SHALL COME:

February 27, 2012

U.S. PATENT: 7,462,645
ISSUE DATE: December 09, 2008

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(12) **United States Patent**
Chaudry et al.

(10) **Patent No.:** **US 7,462,645 B2**
(45) **Date of Patent:** ***Dec. 9, 2008**

(54) **BRONCHODILATING BETA-AGONIST
COMPOSITIONS AND METHODS**

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(*) Notice: Subject to any disclaimer, the term of this
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(51) **Int. Cl.**
A61K 31/135 (2006.01)

(52) **U.S. Cl.** **514/653**

(58) **Field of Classification Search** None
See application file for complete search history.

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(57) **ABSTRACT**

Bronchodilating compositions and methods are provided.
The compositions are intended for administration as a nebu-
lized aerosol. In certain embodiments, the compositions con-
tain formoterol, or a derivative thereof. Methods for treat-
ment, prevention, or amelioration of one or more symptoms
of bronchoconstrictive disorders using the compositions pro-
vided herein are also provided.

9 Claims, No Drawings

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1 BRONCHODILATING BETA-AGONIST COMPOSITIONS AND METHODS

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/887,785, filed Jul. 9, 2004, which, in turn claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 60/486,386, filed Jul. 10, 2003, entitled "BRONCHODILATING β -AGONIST COMPOSITIONS AND METHODS." The disclosure of each of the above-referenced applications is incorporated by reference herein in its entirety.

FIELD

Compositions and methods are provided relating to treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders. In particular, the compositions and methods herein include formoterol, and/or derivatives thereof. The compositions are propellant-free, sterile unit dose or multidisc inhalation solutions intended for administration via mobilization.

BACKGROUND

Bronchoconstrictive disorders affect millions worldwide. Such disorders include asthma (including bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness), chronic bronchitis and other chronic obstructive pulmonary diseases. Compounds having β_2 -adrenoreceptor agonist activity have been developed to treat these conditions. Such compounds include, but are not limited to, Ablution (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxyl-1,3-benzenedimethanol); Bambuterol (dimethylcarbamate acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenyl ester); Bitolterol (4-methyl benzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenyl ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxyl-2-((1-methyl ethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetra hydro-1-(3,4,5-trimethoxyphenyl)methyl)-6,7-isoquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzene methanol); Fenoterol (5-(1-hydroxyl-2-((2-(4-hydroxyphenyl)-1-methyl ethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxyl-5-((1RS)-1-hydroxyl-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethylamino)ethyl)formability); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-ethyl ethyl)amino)methyl)benzene-methanol); Hexoprenaline (4,4'-(1,6-hexanediy)l)-bis(imino-1-hydroxyl-2,1-ethane-idiyl))bis-1,2-benzenediol; Isoetharine (4-(1-hydroxyl-2-((1-methyl ethyl)amino)butyl)-1,2-benzenediol); Isoprinosine (4-(1-hydroxyl-2-((1-methyl ethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxyl-2-((1-methyl ethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(pyridine)ethoxy)hexyls)-amino)methyl)benzene methanol); Pirbuterol (α^5 -(((1,1-dimethylethyl)amino)methyl)-3-hydroxyl-2,6-pyridine methanol); Procter (((R*,S*)-(\pm)-8-hydroxyl-5-(1-hydroxyl-2-((1-methyl ethyl)amino)butyl)-2 (1H)-quinolinone); Reporter ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)propyl)-3,7-dihedron-1,3-diethyl-1H-urine-2,6-dione); Rimier (4-(hydroxyl-2-piperidiny)methyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxyl-1,3-

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benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyls)amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-diethyl-ethyl)amino)methyl)benzene methanol); and TA-2005 (8-hydroxyl-5-((1R)-1-hydroxyl-2-(N-((1R)-2-(4-methoxyphenyl)-1-methyl ethyl)amino)ethyl)carbostyryl hydrochloride).

These compounds are typically formulated for inhalation therapy. Aqueous or liquid formulations are preferred over solid formulations. Powdered formulations are more difficult to administer, particularly to the young and elderly who are most often the patients in need of such therapy. Compounds, such as formoterol are not adequately stable in aqueous solutions to be formulated as liquids. Hence there is a need for formulations of compounds, such as formoterol, in a form that can be conveniently administered and that are stable for extended periods of time.

SUMMARY

Compositions and methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders are provided. The compositions provided herein are stable solutions of a bronchodilating agent, or a derivative thereof, in a pharmacologically suitable fluid that contains water, that are stable during long term storage. The compositions are suitable for direct administration to a subject in need thereof. Pharmacologically suitable fluids include, but are not limited to, polar fluids, including portico fluids. In certain embodiments herein, the compositions are aqueous solutions.

The compositions provided herein possess an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C. and greater than or equal to 1, 2 or 3 years storage time at 5° C. In certain of these embodiments, using Arrhenius kinetics, >80% or >85% or >90% or >95% estimated bronchodilating agent remains after such storage. These compositions are particularly useful for administration via mobilization. In certain embodiments herein, the subject is a mammal. In other embodiments, the subject is a human.

The compositions provided herein are formulated to remain stable over a relatively long period of time. For example, the compositions provided herein are stored between -15° C. and 25° C., or between 2° C. and 8° C., and remain stable for the desired time. In one embodiment, the compositions are stored at 5° C. In other embodiment, the compositions are stored at 25° C.

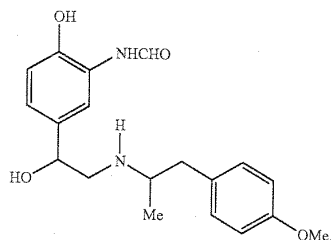
Among the bronchodilating agents for use herein are Ablution (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxyl-1,3-benzenedimethanol); Bambuterol (dimethylcarbamate acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenyl ester); Bitolterol (4-methyl benzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenyl ester); Broxaterol (3-bromo- α -(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxyl-2-((1-methyl ethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetra hydro-1-(3,4,5-trimethoxyphenyl)methyl)-6,7-isoquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzene methanol); Fenoterol (5-(1-hydroxyl-2-((2-(4-hydroxyphenyl)-1-methyl ethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxyl-5-((1RS)-1-hydroxyl-2-(((1RS)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)ethyl)formability); (R,R)-Formoterol; (S,S)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methyl ethyl)amino)methyl)benzene-methanol); Hexoprenaline

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(4,4'-(1,6-hexanediyl)-bis(imino(1-hydroxyl-2,1-ethanediyl))-bis-1,2-benzenediol); Isoetharine (4-(1-hydroxyl-2-((1-methyl ethyl)amino)-butyl)-1,2-benzenediol); Isoprinosine (4-(1-hydroxyl-2-((1-methyl ethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxyl-2-((1-methyl ethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(2-pyridine)ethoxy)hexyl)-amino)methyl)benzene methanol); Pirbuterol (α^6 -(((1,1-dimethyl ethyl)amino)methyl)-3-hydroxyl-2,6-pyridine methanol); Procter (((R*,S*)-(\pm)-8-hydroxyl-5-(1-hydroxyl-2-((1-methyl ethyl)amino)butyl)-2(1H)-quinolinone); Reporter ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)propyl)-3,7-dihedron-1,3-diethyl-1H-urine-2,6-done); Rimier (4-(hydroxyl-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)-amino)methyl)-4-hydroxyl-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)-amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-diethyl-ethyl)amino)methyl)benzene methanol); and TA-2005 (8-hydroxyl-5-((1R)-1-hydroxyl-2-N-((1R)-2-(4-metonymphenyl)-1-methyl ethyl)amino)ethyl)carbostyrylhydrochloride).

Of particular interest herein is formatter, having the formula:



Formatter for use in the compositions and methods provided herein includes 2-hydroxyl-5-((1RS)-1-hydroxyl-2-(((1RS)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)ethyl)formability; or a stereoisomer thereof, and also includes the single enantiomers 2-hydroxyl-5-((1S)-1-hydroxyl-2-(((1S)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)ethyl)formability and 2-hydroxyl-5-((1R)-1-hydroxyl-2-(((1R)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)ethyl)formability.

In certain embodiments, the compositions are administered via mobilization. Administration of a nebulizer aerosol is preferred over the use of dry powders for inhalation in certain subject populations, including pediatric and geriatric groups.

In one embodiment, the compositions for use in the methods provided herein contain a pharmaceutically acceptable derivative of formatter. In another embodiment, the compositions for use in the methods provided herein contain a pharmaceutically acceptable salt of formatter. Pharmaceutically acceptable salts include, but are not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, maltase, tart rates, citrates, acerbates, succinctness, butyrate's, vale rates and fumigates. In one embodiment, the compositions for use in the methods provided herein contain formatter fumigate or formatter fumigate dehydrate. In another embodiment, the compositions for use in the methods provided herein contain formatter tart rate.

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Also provided herein are combinations containing a composition provided herein and a nebulizer. The combinations can be packaged as kits, which optionally contain other components, including instructions for use of the nebulizer. Any nebulizer is contemplated for use in the kits and methods provided herein. In particular, the nebulizers for use herein nebulizer liquid formulations, including the compositions provided herein, containing no propellant. The nebulizer may produce the nebulizer mist by any method known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or vibration. The nebulizer may further have an internal baffle. The internal baffle, together with the housing of the nebulizer, selectively removes large droplets from the mist by impaction and allows the droplets to return to the reservoir. The fine aerosol droplets thus produced are entrained into the lung by the inhaling air/oxygen.

Methods for the treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, including, but not limited to, asthma, including, but not limited to, bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness; chronic bronchitis; and other chronic obstructive pulmonary diseases are provided. The methods involve administering an effective amount of a pharmaceutical composition provided herein to a subject in need of such treatment.

Articles of manufacture, containing packaging material, a composition provided herein, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, are also provided.

DETAILED DESCRIPTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, formatter refers to 2-hydroxyl-5-((1RS)-1-hydroxyl-2-(((1RS)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)ethyl)formability; or a stereoisomer thereof. The term formatter also refers to the single enantiomers 2-hydroxyl-5-((1S)-1-hydroxyl-2-(((1S)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)ethyl)formability ((S,S)-formatter) and 2-hydroxyl-5-((1R)-1-hydroxyl-2-(((1R)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)-ethyl)formability ((R,R)-formatter).

As used herein, formatter fumigate refers to a salt of formatter having the formula (formatter)/2 fumigate.

As used herein, formatter free base refers to the neutral, anhydrous form of formatter. Thus, a recitation that a composition contains, e.g., 20 μ g/mL of formatter free base means that the composition contains 20 μ g/mL of neutral, anhydrous formatter. Such compositions may be prepared using a derivative of formatter.

As used herein, an aerosol is liquid or particulate matter dispersed in air. Aerosols include dispersions of liquids, including aqueous and other solutions, and solids, including powders, in air.

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As used herein, a nebulizer solution refers to a solution that is dispersed in air to form an aerosol. Thus, a nebulizer solution is a particular form of an aerosol.

As used herein, a nebulizer is an instrument that is capable of generating very fine liquid droplets for inhalation into the lung. Within this instrument, the mobilizing liquid or solution is atomized into a mist of droplets with a broad size distribution by methods known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or a vibrating orifice. Nebulizers may further contain, e.g., a baffle which, along with the housing of the instrument, selectively removes large droplets from the mist by impaction. Thus, the mist inhaled into the lung contains fine aerosol droplets.

As used herein, a pharmacologically suitable fluid is a solvent suitable for pharmaceutical use which is not a liquefied propellant gas. Exemplary pharmacologically suitable fluids include polar fluids, including portico fluids such as water.

As used herein, a kit refers to one or more items, including, but not limited to, compounds, compositions, combinations, instruments and devices, suitably packaged for use. Kits provided herein optionally contain instructions for use.

As used herein, a combination refers to any association between two or among more items.

As used herein, fluid refers to any composition that can flow. Fluids thus encompass compositions that are in the form of semi-solids, pastes, solutions, aqueous mixtures, gels, lotions, creams and other such compositions.

As used herein, a mixture is a mutual incorporation of two or more substances, without chemical union, the physical characteristics of each of the components being retained.

As used herein, the stability of a composition provided herein refers to the length of time at a given temperature that is greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient, e.g., formater, is present in the composition. Thus, for example, a composition that is stable for 30 days at 25° C. would have greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient present in the composition at 30 days following storage at 25° C.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enroll ethers, enroll esters, acids, bases, solvates, hydrates or prod rugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such dramatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prod rugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chlorpromazine, chorine, ammonia, diethanolamine and other hydroxy-alkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrimiding-1'-ylmethylbenzimidazole, diethylamide and other alkyl amines, pauperizing and tries(hydroxymethyl) amino methane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, maltase, tart rates, citrates, acerbates, succinctness, butyrate's, vale rates and fumigates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alchemy, alkynes, aryl, heteroaryl, a alkyl, heteroaralkyl, cyclically and heterocyclic esters of

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acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphoric acids, sulfuric acids, sulfuric acids and moronic acids. Pharmaceutically acceptable enroll ethers include, but are not limited to, derivatives of formula $C=C(OR)$ where R is hydrogen, alkyl, alchemy, alkynes, aryl, heteroaryl, a alkyl, heteroaralkyl, cyclically and heterocyclic. Pharmaceutically acceptable enroll esters include, but are not limited to, derivatives of formula $C=C(OC(O)R)$ where R is hydrogen, alkyl, alchemy, alkynes, aryl, heteroaryl, a alkyl, heteroaralkyl, cyclically and heterocyclic. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecule, in certain embodiments 1 to about 100, in other embodiments 1 to about 10, in further embodiments one to about 2, 3 or 4, solvent or water molecules. Formatter salts and hydrates are used in certain embodiments herein.

As used herein, treatment means any manner in which one or more of the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating cancer.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, a prod rug is a compound that, upon in vivo administration, is metabolized or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prod rug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prod rug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can design prod rugs of the compound (see, e.g., Norgay (1985) Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392).

It is to be understood that the compounds for use in the compositions and methods provided herein may contain choral centers. Such choral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds for use in the compositions provided herein may be enantiomerically pure, or be stereo isomeric or diastereomeric mixtures. It is to be understood that the choral centers of the compounds provided herein may undergo epimerization in vivo. Thus, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization in vivo, to administration of the compound in its (S) form.

As used herein, bronchoconstriction refers to a reduction in the caliber of a bronchus or bronchi.

As used herein, undesired and/or uncontrolled bronchoconstriction refers to bronchoconstriction that results in or from a pathological symptom or condition. Pathological conditions include, but are not limited to, asthma and chronic obstructive pulmonary disease (COPD). Pathological symptoms include, but are not limited to, asthma and COPD.

As used herein, the statement that a composition is stable during "long term storage" means that the composition is suitable for administration to a subject in need thereof when it has an estimated shelf-life of greater than 1, 2 or 3 months usage time at 25° C. and greater than or equal to 1, 2 or 3 years

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storage time at 5° C. In certain embodiments herein, using Arrhenius kinetics, >80% or >85% or >90% or >95% estimated bronchodilating agent remains after such storage.

A. Formoterol

Formoterol (2-hydroxyl-5-((1R)-1-hydroxyl-2-(((1R)-2-(p-methoxyphenyl)-1-methyl ethylamino)ethyl)formability) is derived from adrenaline and, as noted above, is used as a β_2 -stimulator in inhalation therapy of respiratory diseases, particularly for the treatment of bronchial asthma. It has been reported that in patients with reversible obstructive respiratory diseases, formoterol has a bronchodilator effect. This effect has a relatively rapid onset (approximately 1-3 minutes) and a relatively long duration (greater than 12 hours). Formoterol inhibits the release of leukotrienes and other messenger substances involved with inflammation, such as histamines. In addition, formoterol may bring about a hyperglycemic activity.

To date, formoterol has been formulated as a dry powder and administered via devices such as the TURBUHALER® and the AEROLIZER®. See, e.g., Siberia et al. (2000) *Respire. Med.* 94(6):607-611; Lotvall et al. (1999) *Can. Respir. J.* 6(5):412-416; Campbell et al. (1999) *Respire. Med.* 93(4):236-244; Nightingale et al. (1999) *Am. J. Respir. Crit. Care Med.* 159(6):1786-1790; Lecaillon et al. (1999) *Eur. J. Clin. Pharmacol.* 55(2):131-138; Bartow et al. (1998) *Drugs* 55(2):303-322; Ekstrom et al. (1998) *Respire. Med.* 92(8):1040-1045; Ringdal et al. (1998) *Respire. Med.* 92(8):1017-1021; Totterman et al. (1998) *Eur. Respir. J.* 12(3):573-579; Palmqvist et al. (1997) *Eur. Respir. J.* 10(11):2484-2489; Nielsen et al. (1997) *Eur. Respir. J.* 10(9):2105-2109; Ullman et al. (1996) *Allergy* 51(10):745-748; Selroos et al. (1996) *Clin. Immunother.* 6:273-299; and Schreurs et al. (1996) *Eur. Respir. J.* 9(8):1678-1683.

Formoterol is also available as a tablet and a dry syrup in certain areas of the world (e.g., ATOCK®, marketed by Yamanouchi Pharmaceutical Co. Ltd., Japan). Formoterol formulations are also available in other areas (e.g., Europe and U.S.) for propellant-based metered dose inhalers and dry powder inhalers (e.g., TURBUHALER®, AEROLIZER® AN) FORADIL AEROLIZER®). None of these formulations are water based. Sterile, stable, aqueous based inhalation solutions of formoterol for mobilization are not available, nor have they been reported.

In the treatment of bronchoconstrictive diseases, sufficient amount of the inhaled drug should reach their local site of action in order to be efficacious. It is known that different delivery methods and delivery devices have different deposition characteristics. Consequently, under optimal inhalation conditions, doses from different delivery methods and delivery devices result in different delivered doses and different amounts deposited at the active site. The actual dose reaching the active site also depends upon the amount of drug particles included in the delivered dose and the inhalation characteristics of the patient. No correlation between the amount of drug administered by dry powder inhalers (DPIs) or metered dose inhalers (MDIs) and the actual amount that gets deposited at the active site has been established so far. Nor has a correlation been established between DPI or MDI dosages and mobilization dosages.

Compositions containing formoterol in combination with other active ingredients have been disclosed. See, e.g., U.S. Pat. Nos. 6,004,537, 5,972,919 and 5,674,860 (formoterol and budesonide), U.S. Pat. Nos. 5,668,110, 5,683,983, 5,677,280 and 5,654,276 (formoterol and IL-5 inhibitors), U.S. Pat. No. 6,136,603 (formoterol and antisense modulators of IL-5), U.S. Pat. No. 5,602,110 (formoterol and milrinone), U.S. Pat. No.

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5,525,623 (formoterol and a striptase inhibitor), U.S. Pat. Nos. 5,691,336, 5,877,191, 5,929,094, 5,750,549 and 5,780,467 (formoterol and a tachykinin receptor antagonist); and International Patent Application Publication Nos. WO 99/00134 (formoterol and roflumilast) and WO 99/36095 (formoterol and a dopamine D₂ receptor agonist).

Other compositions containing formoterol have been disclosed in U.S. Pat. Nos. 5,677,809, 6,126,919, 5,733,526, 6,071,971, 6,068,833, 5,795,564, 6,040,344, 6,041,777, 5,874,481, 5,965,622 and 6,161,536.

U.S. Pat. No. 6,150,418 discloses a "liquid active substance concentrate" containing formoterol in the form of its free base or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as active substance. This "liquid active substance concentrate" is reported to be a concentrated (i.e., greater than 10 mg/mL, preferably 75 to 500 mg/mL) solution or suspension that is stable for a period of several months possibly up to several years without any deterioration in the pharmaceutical quality. This patent teaches that it is the high concentration that allows for the stability of the concentrate. The "liquid active substance concentrate" is not suitable for direct administration to a patient.

U.S. Pat. No. 6,040,344 discloses an aqueous aerosol formulation of formoterol tart rate for use in a nebulizer. This patent states that the formulation disclosed therein is not attractive for long term storage.

B. Compositions for Use in Treatment, Prevention, or Amelioration of One or More Symptoms of Bronchoconstrictive Disorders

Pharmaceutical compositions containing a β_2 -adrenoreceptor agonist for administration via mobilization are provided. The compositions are sterile filtered and filled in vials, including unit dose vials providing sterile unit dose formulations which are used in a nebulizer and suitably nebulizer. Each unit dose vial is sterile and is suitably nebulizer without contaminating other vials or the next dose.

The unit dose vials are formed in a form-fill-seal machine or by any other suitable method known to those of skill in the art. The vials may be made of plastic materials that are suitably used in these processes. For example, plastic materials for preparing the unit dose vials include, but are not limited to, low density polyethylene, high density polyethylene, polypropylene and polyesters. In one embodiment, the plastic material is low density polyethylene.

In one embodiment, the β_2 -adrenoreceptor agonist is formoterol, or a pharmaceutically acceptable derivative thereof. In other embodiments, the formoterol for use in the compositions provided herein is formoterol fumigate. Formoterol refers to 2-hydroxyl-5-((1R)-1-hydroxyl-2-(((1R)-2-(p-methoxyphenyl)-1-methyl ethylamino)ethyl)formability; or a stereoisomer thereof. The term formoterol also refers herein to the single enantiomers 2-hydroxyl-5-((1S)-1-hydroxyl-2-(((1S)-2-(p-methoxyphenyl)-1-methyl ethylamino)ethyl)formability and 2-hydroxyl-5-((1R)-1-hydroxyl-2-(((1R)-2-(p-methoxyphenyl)-1-methyl ethylamino)ethyl)formability.

In certain embodiments, the compositions contain formoterol fumigate at a concentration of about 0.1 μ g/mL up to about 150 μ g/mL, or 0.1 μ g/mL up to 150 μ g/mL. In further embodiments, the compositions contain formoterol fumigate at a concentration of about 0.1 μ g/mL up to about 100 μ g/mL, or 0.1 μ g/mL up to 100 μ g/mL. The formoterol fumigate is formulated, in certain compositions provided herein, at a concentration of about 0.1 μ g/mL up to 50 μ g/mL, or 0.1 μ g/mL up to 50 μ g/mL. In further embodiments, the compositions contain formoterol fumigate at a concentration of about 0.1 μ g/mL

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up to about 40 $\mu\text{g/mL}$, or 0.1 $\mu\text{g/mL}$ up to 40 $\mu\text{g/mL}$. In further embodiments, the compositions contain formatter fumigate at a concentration of about 0.1 $\mu\text{g/mL}$ up to about 20 $\mu\text{g/mL}$, or 0.1 $\mu\text{g/mL}$ up to 20 $\mu\text{g/mL}$. The formatter fumigate is formulated, in other compositions provided herein, at a concentration of about 40 $\mu\text{g/mL}$, or 40 $\mu\text{g/mL}$. In further embodiments, the compositions contain formatter fumigate at a concentration of about 35 $\mu\text{g/mL}$, or 35 $\mu\text{g/mL}$. In other embodiments, the compositions contain formatter fumigate at a concentration of about 30 $\mu\text{g/mL}$, or 30 $\mu\text{g/mL}$. In other embodiments, the compositions contain formatter fumigate at a concentration of about 25 $\mu\text{g/mL}$, or 25 $\mu\text{g/mL}$. In further embodiments, the compositions contain formatter fumigate at a concentration of about 20 $\mu\text{g/mL}$, or 20 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter fumigate at a concentration of about 15 $\mu\text{g/mL}$, or 15 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter fumigate at a concentration of about 12 $\mu\text{g/mL}$, or 12 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter fumigate at a concentration of about 10 $\mu\text{g/mL}$, or 10 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter fumigate at a concentration of about 8 $\mu\text{g/mL}$, or 8 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter fumigate at a concentration of about 5 $\mu\text{g/mL}$, or 5 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter fumigate at a concentration of about 2.5 $\mu\text{g/mL}$, or 2.5 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter fumigate at a concentration of about 1 $\mu\text{g/mL}$, or 1 $\mu\text{g/mL}$.

In certain embodiments, the compositions contain formatter free base at a concentration of about 0.08 $\mu\text{g/mL}$ up to about 128 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 128 $\mu\text{g/mL}$. In further embodiments, the compositions contain formatter free base at a concentration of about 0.08 $\mu\text{g/mL}$ up to about 86 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 86 $\mu\text{g/mL}$. The formatter free base is formulated, in certain compositions provided herein, at a concentration of about 0.08 $\mu\text{g/mL}$ up to 43 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 43 $\mu\text{g/mL}$. In further embodiments, the compositions contain formatter free base at a concentration of about 0.08 $\mu\text{g/mL}$ up to 34 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 34 $\mu\text{g/mL}$. In further embodiments, the compositions contain formatter free base at a concentration of about 0.08 $\mu\text{g/mL}$ up to about 26 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 26 $\mu\text{g/mL}$. The formatter free base is formulated, in other compositions provided herein, at a concentration of about 0.08 $\mu\text{g/mL}$ up to about 17 $\mu\text{g/mL}$, or 0.08 $\mu\text{g/mL}$ up to 17 $\mu\text{g/mL}$. In further embodiments, the compositions contain formatter free base at a concentration of about 34 $\mu\text{g/mL}$, or 34 $\mu\text{g/mL}$. In Her embodiments, the compositions contain formatter free base at a concentration of about 30 $\mu\text{g/mL}$, or 30 $\mu\text{g/mL}$. In other embodiments, the compositions contain formatter free base at a concentration of about 25.6 $\mu\text{g/mL}$, or 25.6 $\mu\text{g/mL}$. In further embodiments, the compositions contain formatter free base at a concentration of about 21.4 $\mu\text{g/mL}$, or 21.4 $\mu\text{g/mL}$. In further embodiments, the compositions contain formatter free base at a concentration of about 17 $\mu\text{g/mL}$, or 17 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter free base at a concentration of about 13 $\mu\text{g/mL}$, or 13 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter free base at a concentration of about 10 $\mu\text{g/mL}$, or 10 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter free base at a concentration of about 9 $\mu\text{g/mL}$, or 9 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter free base at a concentration of about 7 $\mu\text{g/mL}$, or 7 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter free base at a concentration of about 4 $\mu\text{g/mL}$, or 4 $\mu\text{g/mL}$. In another embodiment, the compositions contain formatter free base at a concentration of about 2 $\mu\text{g/mL}$, or 2 $\mu\text{g/mL}$. In

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another embodiment, the compositions contain formatter free base at a concentration of about 0.8 $\mu\text{g/mL}$, or 0.8 $\mu\text{g/mL}$.

The volume of formatter inhalation solution nebulizer depends on the nebulizer used. In certain embodiments, the volume is from about 0.1 mL up to about 3 mL, or 0.1 mL up to 3 mL. In other embodiments, the volume is about 2 mL, or 2 mL. In other embodiments, the volume is about 1 mL, or 1 mL. In other embodiments, the volume is about 0.5 mL, or 0.5 mL.

The compositions containing the β_2 -adrenoreceptor agonist, including formatter, are formulated with a pharmacologically suitable fluid. Pharmacologically suitable fluids include, but are not limited to, polar solvents, including, but not limited to, compounds that contain hydroxyl groups or other polar groups. Such solvents include, but are not limited to, water or alcohols, such as ethanol, isopropanol, and glycols including propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol and polyoxyethylene alcohols.

Polar solvents also include portico solvents, including, but not limited to, water, aqueous saline solutions with one or more pharmaceutically acceptable salt(s), alcohols, glycols or a mixture thereof. For a saline solution as the solvent or as a component thereof, particularly suitable salts are those which display no or only negligible pharmacological activity after administration.

In the embodiments herein, the compositions have a pI of about 2.0 to about 8.0, or 2.0 to 8.0. In other embodiments, the compositions have a pH of about 4.0 to about 6.0, or 4.0 to 6.0. In other embodiments, the pH is about 4.5 to about 5.5, or 4.5 to 5.5. In certain of the above embodiments, the compositions are formulated at a pH of about 4, 4.4 or 4.6 up to about 5.5, 5.7 or 6; or 4, 4.4 or 4.6 up to 5.5, 5.7 or 6. In other embodiments, the pH is about 5.0, or 5.0. It has been found that the rate constant for decomposition of an aqueous solution of formatter is dependent on pH. The rate constant (k_{obs}) at 60° C. at a pH of 3, 4, 5 and 7 is approximately 0.62, 0.11, 0.044 and 0.55 day. sup.-1, respectively. Therefore, the decomposition of formatter in aqueous solution at 60° C. at a buffer concentration of 5 mM and an ionic strength of 0.05 is slowest at a pH of about 5.0, or 5.0.

The solubility of formatter in aqueous solution has been found to be dependent on pH. Thus, at a pH of between about 5 and about 7, the aqueous solubility of formatter at ambient temperature is approximately 2.2 mg/mL. At a pH of about 4, the aqueous solubility of formatter at ambient temperature is approximately 3 mg/mL, while at a pH of about 3, the aqueous solubility of formatter at ambient temperature is about 4.8 mg/mL. The solubility of formatter in pure water, for example, high performance liquid chromatography (HPLC) water, at ambient temperature is approximately 2 mg/mL.

In other of the above embodiments, the compositions further contain a buffer, including, but not limited to, citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, acidulate, citrate, colliding, format, male ate, Mulvane, phosphate, Rideau-Ward, succinct, citrate-phosphate-borate (Teorell-Stanhagen), vernal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris-(hydroxymethyl)methane), ADA (N-(2-actinide)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BISTRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamine)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid),

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HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)-butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamine)-2-hydroxypropanesulfonic acid), TRIZMA® (tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N-(2-hydroxypropanesulfonic acid), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N-(3-propanesulfonic acid), TRICINE (N-tris(hydroxyl-methyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)lysine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanedisulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), AMPD (2-amino-2-methyl-1,3-propanediol), and/or any other buffers known to those of skill in the art. In one embodiment, the buffer is citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer. In another embodiment, the buffer is a citrate buffer (citric acid/sodium citrate). The buffer concentration has been found to affect the stability of the composition. Buffer concentrations for use include from about 0 or 0.01 mM to about 150 mM, or 0 or 0.01 mM to 150 mM. In another embodiment, the buffer concentration is about 1 mM to about 20 mM, or 1 mM to 20 mM. In one embodiment, the buffer concentration is about 5 mM, or 5 mM. In other embodiments, the buffer concentration is about 1 mM to about 50 mM, or 1 mM to 50 mM. In one embodiment, the buffer concentration is about 20 mM, or 20 mM. The kinetic-pH profile of formatter is dependent on buffer concentration. At low and approximately neutral conditions, increasing the buffer concentration from 5 mM to 20 mM increased the rate constant of decomposition significantly. However, no noticeable differences in rate constant were observed in the pH region of about 4.5 to about 5.5, with increasing buffer concentration from 5 mM to 20 mM. The particular buffer and buffer concentration of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, e.g., the Examples).

The ionic strength of the compositions provided herein also has been found to affect the stability of the composition. Ionic strengths of the compositions provided herein are from about 0 to about 0.4, or 0 to 0.4. In another embodiment, the ionic strength of the compositions provided is about 0.05 to about 0.16, or 0.05 to 0.16. Compositions having a lower ionic strength exhibit improved stability over formulations having higher ionic strength. The rate constant of decomposition was essentially the same at ionic strength 0.05 to 0.1, but increased to some extent at ionic strength of 0.2. The particular ionic strength of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, e.g., the Examples).

In embodiments where the pharmacologically suitable fluid is a saline solution, tonicity adjusting agents may be added to provide the desired ionic strength. Tonicity adjusting agents for use herein include those which display no or only negligible pharmacological activity after administration. Both inorganic and organic tonicity adjusting agents may be used in the compositions provided herein. Tonicity adjusting agents include, but are not limited to, ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bis-muth sodium tart rate, boric acid, calcium chloride, calcium disodium edentate, calcium gliolate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edentate disodium, edentate disodium monohydrate, fluoresce in

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sodium, fructose, galaxies, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, manifold, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfate, sodium borate, sodium bromide, sodium acidulate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tart rate, sodium hyposulfite, orbital, sucrose, tartaric acid, triethanolamine, urea, urethane, Uri dine and zinc sulfate. In certain embodiments, the tonicity adjusting agent is sodium chloride. In these embodiments, the pharmacologically suitable fluid is aqueous saline.

The storage temperature of the compositions provided herein also has been found to affect the stability of the composition. Compositions stored at a lower temperature exhibit improved stability over formulations stored at higher temperatures. The effect of temperature on the rate constant of decomposition at pH 5, a buffer concentration of 5 mM, and an ionic strength of 0.05, was linear according to Arrhenius kinetics, i.e., when $\ln k_{obs}$ was plotted against $1/T$, where T is the temperature in degree Kelvin.

The estimated shelf-life of formatter in the compositions provided herein is significantly greater than that reported for known formatter compositions. The estimated shelf-life of formatter in the compositions provided herein is about 6.2 years, at 5° C. and about 7.5 months, or at 25° C. The estimated formatter concentrations in the compositions provided herein as a function of storage time at 5° C. and usage time at 25° C. was determined. It is estimated that greater than 90% of the initial formatter present in the composition remains after 3 months of usage time at 25° C. and 3 years of storage time at 5° C. as well as after 0.5 months of usage time at 25° C. and 1 year of storage time at 5° C.

In one embodiment, the compositions provided herein are prepared containing formatter fumigate at a nominal concentration of 0.1 mg/mL at the indicated pH and citric acid/phosphate buffer concentrations. The solutions were stored at 60° C. In these compositions, formatter is relatively more stable at a pH from about 4 to about 5, and is also more stable at lower buffer concentration.

The compositions provided herein also may include recipients and additives. The particular recipient or additive for use in the compositions for long term storage provided herein may be determined empirically using methods well known to those of skill in the art (see, e.g., the Examples). Recipients and additives are any pharmacologically suitable and therapeutically useful substance which is not an active substance. Recipients and additives generally have no pharmacological activity, or at least no undesirable pharmacological activity. The recipients and additives include, but are not limited to, surfactants, stabilizers, completing agents, antioxidants, or preservatives which prolong the duration of use of the finished pharmaceutical formulation, flavorings, vitamins, or other additives known in the art. Completing agents include, but are not limited to, ethylenediaminetetraacetic acid (EDTA) or a salt thereof, such as the disodium salt, citric acid, nitrilotriacetic acid and the salts thereof. In one embodiment, the completing agent is EDTA. Preservatives include, but are not limited to, those that protect the solution from contamination with pathogenic particles, including benzalkonium chloride or benzoic acid, or benzoates such as sodium benzoate. Antioxidants include, but are not limited to, vitamins, provitamins, ascorbic acid, vitamin E or salts or esters thereof

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The compositions provided herein also may include a co solvent, which increases the solubility of additives or the active ingredient(s). The particular co solvent for use in the compositions for long term storage provided herein may be determined empirically using methods well known to those of skill in the art. Co solvents for use herein include, but are not limited to, hydroxylated solvents or other polar solvents, such as alcohols such as isopropyl alcohol, glycols such as propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol, and polyoxyethylene alcohols.

C. Preparation of Compounds for Use in the Compositions

The preparation of the compounds used in the compositions provided herein is described below. Any such compound or similar compound may be synthesized according to a method discussed in general below or by only minor modification of the methods by selecting appropriate starting materials.

Formoterol may be prepared according to the method disclosed in U.S. Pat. No. 3,994,974. Briefly, 4-benzyl-3-nitro- α -bromoacetophenone is reacted with N-benzyl-N-(1-methyl-2-p-methoxyphenylethyl)amine to form the α -aminoacetophenone. This compound was subjected to the following series of reactions: (i) reduction of the ketene with sodium borohydride; (ii) reduction of the nitro group with aqueous hydrochloric acid and iron powder; (iii) amine formulation with acetic anhydride and formic acid; and (iv) catalytic reduction over 10% palladium on carbon to afford formoterol free base. Crystallization of the $\frac{1}{2}$ fumigate salt from ethanol provides (formoterol) $\frac{1}{2}$ fumigate.

The individual enantiomers of formoterol, 2-hydroxyl-5-((1S)-1-hydroxyl-2-(((1S)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)ethyl)formamide and 2-hydroxyl-5-((1R)-1-hydroxyl-2-(((1R)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)ethyl)formamide, may be prepared by the method disclosed in U.S. Pat. No. 6,040,344. Briefly, reaction of optically pure 4-benzyl-3-formamidostyrene oxide with an optically pure 4-methoxy- α -methyl-N-(phenyl methyl)benzeneethanamine, followed by debenzilation, affords the desired enantiomer of formoterol. Debentilation may be accomplished by reduction with hydrogen gas in the presence of a noble metal catalyst, such as palladium on carbon.

The required optically pure 4-benzyl-3-formamidostyrene oxide may be prepared from 4-benzyl-3-nitro- α -bromoacetophenone by (i) reduction with orange in the presence of an optically pure aminoindanol, (ii) hydrogenation over platinum oxide catalyst, (iii) formulation with formic acid and acetic anhydride, and (iv) peroxide formation in the presence of potassium carbonate.

The required optically pure 4-methoxy- α -methyl-N-(phenyl methyl)benzeneethanamine may be prepared from 4-methoxyphenylacetone by (i) reductive lamination with benzyl amine in the presence of hydrogen and a platinum catalyst, and (ii) crystallization of the desired optically pure amine from the resulting racemes mixture as its mandolin acid salt.

D. Formulation of Pharmaceutical Compositions

The compositions provided herein are prepared by procedures well known to those of skill in the art. For example, a formoterol fumigate solution may be prepared by the procedure of EXAMPLE 1. Briefly, a buffer solution having a pH and ionic strength of interest herein is prepared. In one embodiment, the buffer is a mixture of citric acid and sodium citrate, with sodium chloride added to achieve the desired ionic strength. Formoterol fumigate dehydrate is added to the buffer solution with agitation to produce a solution of the

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desired formoterol concentration. Exemplary formoterol concentrations is 0.0021 kg formoterol imamate dehydrate/100 kg water.

E. Evaluation of the Activity of the Compositions

Standard physiological, pharmacological and biochemical procedures are available for testing the compositions provided herein to identify those that possess bronchodilator activity.

In vitro and in vivo assays that may be used to evaluate bronchodilator activity are well known to those of skill in the art. See also, e.g., U.S. Pat. Nos. 3,994,974, and 6,068,833; German Patent No. 2,305,092; Kaumann et al. (1985) Naunyn-Schmied Arch. Pharmacol. 331:27-39; Lemoine et al. (1985) Naunyn-Schmied Arch. Pharmacol. 331:40-51; Tomioka et al. (1981) Arch. Int. Pharmacodyn. 250:279-292; Dellamary et al. (2000) Pharm. Res. 17(2):168-174; Rico-Mendez et al. (1999) Rev. Alerg. Mex. 46(5):130-135; Seberova et al. (2000) Respir. Med. 94(6):607-611; Lotvall et al. (1999) Can. Respir. J. 6(5):412-416; Campbell et al. (1999) Respir. Med. 93(4):236-244; Nightingale et al. (1999) Am. J. Respir. Crit. Care Med. 159(6):1786-1790; Lecaillon et al. (1999) Eur. J. Clin. Pharmacol. 55(2):131-138; Bartow et al. (1998) Drugs 55(2):303-322; Ekstrom et al. (1998) Respir. Med. 92(8):1040-1045; Ringdal et al. (1998) Respir. Med. 92(8):1017-1021; Totterman et al. (1998) Eur. Respir. J. 12(3):573-579; Palmqvist et al. (1997) Eur. Respir. J. 10(9):2484-2489; Nielsen et al. (1997) Eur. Respir. J. 10(9):2105-2109; Ullman et al. (1996) Allergy 51(10):745-748; Selroos et al. (1996) Clin. Immunother. 6:273-299; and Schreurs et al. (1996) Eur. Respir. J. 9(8):1678-1683.

F. Methods of Treatment of Bronchoconstrictive Disorders

The compositions provided herein are used for treating, preventing, or ameliorating one or more symptoms of a bronchoconstrictive disorders in a subject. In one embodiment, the method includes administering to a subject an effective amount of a composition containing a bronchodilating agent, including, but not limited to, formoterol, whereby the disease or disorder is treated or prevented. The subject treated is, in certain embodiments, a mammal. The mammal treated is, in certain embodiments, a human.

In another embodiment, the method provided herein includes oral administration of a composition provided herein. In certain embodiments herein, the composition is directly administered to a subject in need of such treatment via mobilization without dilution or other modification of the composition prior to administration.

The methods for treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders, in another embodiment, further include administering one or more of (a), (b), (c) or (d) as follows: (a) a β_2 -adrenoreceptor agonist; (b) a dopamine (D_2) receptor agonist; (c) a prophylactic therapeutic, such as a steroid; or (d) an anticholinergic agent; simultaneously with, prior to or subsequent to the composition provided herein.

β_2 -Adrenoreceptor agonists for use in combination with the compositions provided herein include, but are not limited to, Albuterol (α^1 -(((1,1-dimethylethyl)amino)methyl)-4-hydroxyl-1,3-benzenedimethanol); Bambuterol (dimethylcarbamate 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenyl ester); Bitolterol (4-methyl benzoic acid 4-(2-((1,1-dimethylethylamino)-1-hydroxyethyl)-1,2-phenyl ester); Bixaterol (3-bromo- α -(((1,1-dimethylethylamino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxyl-2-((1-methyl ethyl)amino)ethyl)-1,2-benzenediol); Trimetoquinol (1,2,3,4-tetra hydro-1-((3,4,5-

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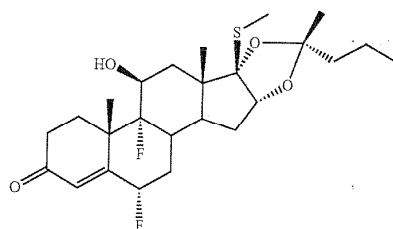
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trimethoxyphenyl)methyl)-6,7-isoquinolinediol); Clenbuterol (4-amino-3,5-dichloro- α -(((1,1-dimethylethyl)amino)methyl)benzene methanol); Fenoterol (5-(1-hydroxyl-2-((2-(4-hydroxyphenyl)-1-methyl ethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxyl-5-((1RS)-1-hydroxyl-2-(((1RS)-2-(p-methoxyphenyl)-1-methyl ethyl)amino)ethyl)-formability); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy- α -(((2-(4-methoxyphenyl)-1-methyl ethyl)amino)methyl)benzene methanol); Hexoprenaline (4,4'-(1,6-hexanedyl)-bis(imino (-1-hydroxyl-2,1-ethanedyl)))bis-1,2-benzenediol); Isoetarine (4-(1-hydroxyl-2-((1-methyl ethyl)amino)butyl)-1,2-benzenediol); Isoprinosine (4-(1-hydroxyl-2-((1-methyl ethyl)amino)ethyl)-1,2-benzenediol); Metaproterenol (5-(1-hydroxyl-2-((1-methyl ethyl)amino)ethyl)-1,3-benzenediol); Picumeterol (4-amino-3,5-dichloro- α -(((6-(2-(2-pyridine)ethoxy)hexyl)amino)methyl)benzene methanol); Pirbuterol (α^6 -(((1,1-dimethylethylamino)methyl)-3-hydroxyl-2,6-pyridine methanol); Procter (((R*,S*)-(\pm)-8-hydroxyl-5-(1-hydroxyl-2-((1-methyl ethyl)amino)butyl)-2 (1H)-quinolinone); Reporter (((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)-propyl)-3,7-dihedron-1,3-diethyl-1H-purine-2,6-dione); Rinniterol (4-(hydroxyl-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((\pm)- α^1 -(((1,1-dimethylethyl)amino)-methyl)-4-hydroxyl-1,3-benzenedimethanol); (R)-Salbutamol; Salmeterol ((\pm)-4-hydroxy- α^1 -(((6-(4-phenylbutoxy)hexyl)amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro- α -(((1,1-dimethylethyl)amino)-methyl)benzene methanol); and TA-2005 (8-hydroxyl-5-((1R)-1-hydroxyl-2-(N-((1R)-2-(4-methoxyphenyl)-1-methyl ethyl)amino)ethyl)carbostyryl hydrochloride).

Dopamine (D_2) receptor agonists include, but are not limited to, Apo morphine ((r)-5,6,6a,7-tetra hydro-6-methyl-4H-dibenzo[de,g]quinoline-10,11-diol); Bromocriptine ((5 α)-2-broom-12'-hydroxyl-2'-(1-methyl-ethyl)-5'-(2-methylpropyl)ergotamine-3',6',18-triure); Cabergoline ((8B)-N-(3-(dimethylamino)propyl)-N-((ethylamine)carbonyl)-6-(2-progeny)ergo line-8-carboxamide); Lisuride (N'-(8 α)-9,10-dihydro-6-methylergolin-8-yl)-N,N-diethyl urea); Peroxide ((8 α)-8-((methylthio)methyl)-6-propylergoline); Leonora (3-hydroxy-L-tryrosine); Pramipexole ((s)-4,5,6,7-tetrahydro-N-sup.6-propyl-2,6-benzothiazole-diamine); Quinpirole hydrochloride (trans-(-)-4aR-4,4a,5,6,7,8,8a,9-octahedron-5-pro-pyl-1H-pyrazolo[3,4-g]quinoline hydrochloride); Ropinirole (4-(2-(dipropylamino)ethyl)-1,3-dihedron-2H-idol-2-one); and Talipexole (5,6,7,8-tetra hydro-6-(2-progeny)-4H-thiazolo[4,5-d]aspen-2-amine). Other dopamine D_2 receptor agonists for use herein are disclosed in International Patent Application Publication No. WO 99/36095.

Prophylactic therapeutics for use in combination therapy herein include steroidal anti-inflammatory agents, including, but not limited to, beclomethasone dipropionate (BDP), beclomethasone monopropionate (BMP), flunisolide, triamcinolone actinide, dexamethasone, tapenade, ciclesonid, rofleponide, mometasone, mometasone furcated (ASMANEX® TWISTHALER™, Schering-Plough Corporation, Kenilworth, N.J.), RPR 106541, having the formula

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fluticasone or fluticasone propionate and budesonide or by way of sodium cromoglycate or nedocromil sodium.

Ant cholinergic agents for use herein include, but are not limited to, ipratropium bromide, oxitropium bromide, atropine methyl nitrate, atropine sulfate, ipratropium, belladonna extract, scopolamine, scopolamine meth bromide, homatropine meth bromide, hyoscyamine, isopropripramide, orphenadrine, benzalkonium chloride, tiotropium bromide and glycopyrronium bromide. In certain embodiments, the compositions contain an ant cholinergic agent, such as ipratropium bromide, at a concentration of about 100 μ g/mL to about 500 μ g/mL, or 100 μ g/mL to 500 μ g/mL. In other embodiments, ipratropium bromide concentration is about 150 μ g/mL to about 350 μ g/mL, or 150 μ g/mL to 350 μ g/mL. In other embodiments, the compositions for use in the methods herein contain ipratropium bromide at a concentration of about 200 μ g/mL to about 300 μ g/mL, or 200 μ g/mL to 300 μ g/mL. In other embodiments, the compositions for use in the methods herein contain ipratropium bromide at a concentration of about 250 μ g/mL, or 250 μ g/mL.

Other active ingredients for use herein in combination therapy, include, but are not limited to, IL-5 inhibitors such as those disclosed in U.S. Pat. Nos. 5,668,110, 5,683,983, 5,677,280 and 5,654,276; antisense modulators of IL-5 such as those disclosed in U.S. Pat. No. 6,136,603; million (1,6-dihedron-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile million lactate; striptase inhibitors such as those disclosed in U.S. Pat. No. 5,525,623; tachykinin receptor antagonists such as those disclosed in U.S. Pat. Nos. 5,691,336, 5,877,191, 5,929,094, 5,750,549 and 5,780,467; leukotriene receptor antagonists such as montelukast sodium (SINGULAR®, R-(E)-1-[[[1-[3-[2-(7-chloral-2-quinolinyl)ethenyl]phenyl]-3-2-(1-hydroxyl-1-methyl ethyl)phenyl]-propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt), 5-lipoxygenase inhibitors such as kiloton (ZYFLO®, Abbott Laboratories, Abbott Park, Ill.), and anti-IgE antibodies such as XOLAIR® (recombinant humanized anti-IgE monoclonal antibody (CGP 51901; IGE 025A; rhuMab-E25), Genentech, Inc., South San Francisco, Calif.).

The bronchoconstrictive disorder to be treated, prevented, or whose one or more symptoms are to be ameliorated is associated with asthma, including, but not limited to, bronchial asthma, allergic asthma and intrinsic asthma, e.g., late asthma and airway hyper-responsiveness; and, particularly in embodiments where an ant cholinergic agent is used, other chronic obstructive pulmonary diseases (COPDs), including, but not limited to, chronic bronchitis, emphysema, and associated cur culminate (heart disease secondary to disease of the

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lungs and respiratory system) with pulmonary hypertension, right ventricular hypertrophy and right heart failure. COPD is frequently associated with cigarette smoking, infections, environmental pollution and occupational dust exposure.

G. Nebulizers

The compositions provided herein are intended for administration to a subject in need of such treatment via mobilization. Nebulizers that nebulizer liquid formulations containing no propellant are suitable for use with the compositions provided herein. The nebulizer can be unit dose or multidisc. Nebulizers are available from, e.g., Pari GmbH (Stamberg, Germany), DeVilbiss Healthcare (Heston, Middlesex, UK), Healthdyne, Vital Signs, Baxter, Allied Health Care, Invacare, Hudson, Omron, Brema, AirSep, Luminscope, Medisana, Siemens, Aerogen, Mountain Medical, Aerosol Medical Ltd. (Colchester, Essex, UK), AFP Medical (Rugby, Warwickshire, UK), Bard Ltd. (Sunderland, UK), Carri-Med Ltd. (Dorking, UK), Plaem Nuiva (Brescia, Italy), Henleys Medical Supplies (London, UK), Intersurgical (Berkshire, UK), Life care Hospital Supplies (Leies, UK), Medic-Aid Ltd. (West Sussex, UK), Medix Ltd. (Essex, UK), Sinclair Medical Ltd. (Surrey, UK), and many others.

Nebulizers for use herein include, but are not limited to, Jet nebulizers (optionally sold with compressors), ultrasonic nebulizers, and others. Exemplary jet nebulizers for use herein include Pari LC plus/ProNeb, Pari LC plus/ProNeb Turbo, Pari LC plus/Dura Neb 1000 & 2000, Pari LC plus/Walhlaler, Parn LC plus/Pari Master, Pari LC star, Omron CompAir XL Portable Nebulizer System (NE-C 18 and JetAir Disposable nebulizer), Omron CompAir Elite Compressor Nebulizer System (NA-C21 and Elite Air Reusable Nebulizer), Pari LC Plus or Pari LC Star nebulizer with Prone Ultra compressor Pulmo-aide, Pulmo-aide LT, Pulmo-aide traveler, Invacare Passport, Inspiration Healthdyne 626, Pulmo-Neb Traveler, DeVilbiss 646, Whisper Jet, Acorn II, Misty-Neb, Allied aerosol, Schuco Home Care, Lexan Plastic Pocet Neb, Side Stream Hand Held Neb, Mobil Mist, Up-Draft, Up-Draft II, T Up-Draft, ISO-NEB, AVA-NEB, Micro Mist, and Plummeted. Exemplary ultrasonic nebulizers for use herein include Micro Air, Ultra Air, Siemens Ultra Nebulizer 145, CompAir, Paleozoic, Scout, 5003 Ultrasonic Neb, 5110 Ultrasonic Neb, 5004 Desk Ultrasonic Nebulizer, Mystique Ultrasonic, Luminscope's Ultrasonic Nebulizer, Medisana Ultrasonic Nebulizer, Microstat Ultrasonic Nebulizer, and MABISMist Hand Held Ultrasonic Nebulizer. Other nebulizers for use herein include 5000 Electromagnetic Neb, 5001 Electromagnetic Neb 5002 Rotary Piston Neb, Lumineb I Piston Nebulizer 5500, AERONEB™ Portable Nebulizer System, AERODOSE™ Inhaler, AeroEclipse Breath Actuated Nebulizer, HALOLITE™ system (Profile Therapeutics), AKITA® systems (InaMed, Germany), Mystic system (BattellePharma), RESPIMAT® (Boehringer Ingelheim), AERtX® (Aradigm), and E-FLOW™ (Pari).

Depending on the nebulizer used, the volume of the formoterol inhalation solution nebulizer in one embodiment, is about 0.1 mL to 3 mL, or 0.1 mL to 3 mL. In another embodiment, the volume is about 2 mL, or 2 mL. In another embodiment, the volume is about 1 mL, or 1 mL. In another embodiment, the volume is about 0.5 mL, or 0.5 mL.

H. Articles of Manufacture

The compositions provided herein may be packaged as articles of manufacture containing packaging material, a composition provided herein, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the

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composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

In one embodiment herein, the compositions are packaged with a nebulizer for direct administration of the composition to a subject in need thereof.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1

Preparation of Formoterol Inhalation Solution Formulation:

Appropriate quantities of the raw materials are weighed for the 100 Kg batch as shown below:

	20 µg/mL*	10 µg/mL*
Formoterol fumarate dihydrate	0.0021 kg	0.00105 kg
Citric acid monohydrate USP	0.135 kg	0.135 kg
Sodium Citrate dihydrate USP	0.400 kg	0.400 kg
Sodium chloride USP	0.785 kg	0.785 kg
Purified water USP	q.s. to 100 kg	q.s. to 100 kg

*Concentration of formoterol fumarate (anhydrous)

In a clean stainless steel (SS) tank fitted with bottom drain, 75% of the required amount of purified water is added. Samples are taken for pH, conductivity, and microbiological testing. Citric acid monohydrate, sodium citrate dehydrate and sodium chloride are added to the tank and mixed for 15 minutes to dissolve. A sample is taken at this point to check pH. Formoterol fumarate dihydrate is added at this point and mixed for about 75 minutes to dissolve all active raw material. Purified water is used to adjust to final volume. The formulation is mixed for an additional 30 minutes and samples for pH and assay are taken based on which the formulation is released for filling. The bulk solution is filled into low density polyethylene (LDPE) vials (2 mL fill) in a form-fill-seal (FFS) machine. The released drug product solution is transferred from the formulation tank through sanitary delivery lines into the FFS machine. The individual vials are over-wrapped with a suitable foil laminate.

EXAMPLE 2

Procedure for Stability Testing of Formoterol Solutions

Stability samples of the solution prepared in EXAMPLE 1 and solution of formoterol fumarate (20 µg/mL) and ipratropium bromide (250 µg/mL) were placed in LDPE vials and stored in stability ovens at accelerated temperatures. At selected time points, aliquots of the samples were removed from the vials. The formoterol concentrations of the samples were analyzed by high performance liquid chromatography.

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Provided herein is the stability data for exemplary formulations containing formoterol and formoterol in combination with ipratropium bromide,

Stability data on formoterol (20 µg/mL) and formoterol fumarate/ipratropium bromide combination (20 µg/mL and 250 µg/mL):

Storage condition	Assay as percent of label claim		
	Formoterol Inhalation solution	Formoterol fumarate/ipratropium bromide inhalation solution	Ipratropium
Initial	100	100.5	101.2
5° C./3 months	96.7	100	101.6
25° C./3 months	94.5	100	101.2

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

What is claimed is:

1. A method of treating undesired and/or uncontrolled bronchoconstriction comprising the steps of:

(a) adding to a nebulizer, from a propellant-free, sterile unit dose in pharmaceutical packaging material about 1 to about 3 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 µg/mL to about 43 µg/mL based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a buffer selected from the group consisting of citric acid/phosphate buffer, acetate buffer, citrate buffer and phosphate buffer at a concentration of from about 1 mM to about 50 mM, said composition having a pH of between about 4.5 and about 5.5; and

(b) directly administering said composition to a subject in need thereof, without dilution or other modification of said prior to administration.

2. A method of treating undesired and/or uncontrolled bronchoconstriction comprising the steps of:

(a) adding to a nebulizer from a propellant-free, sterile unit dose in pharmaceutical packaging material about 1 to about 3 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 µg/mL to about 43 µg/mL based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a

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buffer selected from the group consisting of citric acid/phosphate buffer, acetate buffer, citrate buffer and phosphate buffer at a concentration of from about 1 mM to about 50 mM, said composition having a pH of between about 4.5 and about 5.5 and having an estimated shelf life of greater than 90% after 3 months storage at 25° C. and after 3 years storage at 5° C.; and

(b) directly administering said composition to a subject in need thereof, without dilution or other modification of said prior to administration.

3. A method of treating undesired and/or uncontrolled bronchoconstriction comprising the steps of:

(a) adding to a nebulizer from a propellant-free, sterile unit dose in pharmaceutical packaging material about 2 mL of a pharmaceutical composition comprising formoterol or a salt thereof at a concentration of from about 0.08 µg/mL to about 43 µg/mL based on formoterol free base, in a pharmacologically suitable solution, wherein the composition further comprises water and a citrate buffer at a concentration of from about 1 mM to about 20 mM, said composition having a pH of about 5 and having an estimated shelf life of greater than about 94% after 3 months storage at 25° C. and greater than about 96% after 3 months storage at 5° C.; and

(b) directly administering said composition to a subject in need thereof, without dilution or other modification of said composition prior to administration.

4. The method of treating undesired and/or uncontrolled bronchoconstriction as in any one of claims 1, 2 and 3 wherein said undesired and/or uncontrolled bronchoconstriction is a symptom or condition of asthma.

5. The method of treating undesired and/or uncontrolled bronchoconstriction as in any one of claims 1, 2 and 3 wherein said undesired and/or uncontrolled bronchoconstriction is a symptom or condition of chronic obstructive pulmonary disease.

6. The method as in any one of claims 1 and 2 wherein said buffer is present at a concentration of between about 1 mM and about 20 mM.

7. The method as in any one of claims 1, 2 and 3 wherein said Pharmaceutical packaging material is selected from the group consisting of blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers and syringes.

8. The method of claim 7 wherein said pharmaceutical packaging material is a vial over wrapped with a laminate.

9. The method as in any one of claims 1 and 2, wherein about 2.0 mL of the composition is nebulized.

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**CERTIFICATE OF COMPLIANCE WITH
TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS,
AND TYPE STYLE REQUIREMENTS**

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 13,764 words, excluding the parts of the brief exempted by Federal Rule of Appellate procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate procedure 32(a)(6) because this brief has been prepared in proportionally spaced typeface using Microsoft Word in 14-point Times New Roman font.

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